Comparative Effectiveness of Smoking Cessation Medications among Schizophrenic Smokers

I-Hsuan Wu, M.S.

Department of Pharmaceutical Health Outcomes and Policy

College of Pharmacy

University of Houston

PROJECT SUMMARY

Smoking is a serious public health problem. Tobacco use causes approximately 443,000 premature deaths annually in the United States (US) [1, 2] and 5.4 million worldwide [3]. Schizophrenic patients have higher smoking rates when compared to people in the general population: 72% - 90% vs. 23% [4]. Additionally, they tend to be heavy smokers [5], have much lower smoking cessation rates and higher nicotine dependence level [6, 7].

Smoking cessation is highly recommended by public health department of various organizations and several smoking intervention strategies are available for smokers. During the 1990s, a variety of pharmaceutical cessation aids became available, which include nicotine replacement therapy (NRT) and Bupropion SR [8]. Even more recently, Varenicline was approved as an aid to smoking cessation [9].

Only a few studies regarding smoking cessation have been conducted among this minority population and all of those were with very small sample sizes and were in a rigorously controlled RCT pattern. No head to head comparison trials between cessation medications have been conducted and thus it is unclear which medication is more effective among this population.

Cardiovascular disease is the leading cause of death as a result of smoking, with rates even higher than those by cancer and respiratory disease. Although smoking cessation is associated with substantial health benefits including prevention of cardiovascular diseases, weight gain after quitting is commonly cited [10]. Because of diseases that could result from the weight gain, this is a great concern. Studies report a higher incidence of diabetes or hypertension among smokers that quit compared to those who continue with the smoking habit [11, 12]. Different cessation medications also have different mechanisms of action and it is unclear how

using different regimens can modify the risks of metabolic syndromes for schizophrenic patients. To date, no studies have been conducted among this specific population.

The lifetime risk of suicide among schizophrenic patients is much higher than that in the general population, and suicide is the leading cause of premature death among patients with schizophrenia [13]. The U.S. Food and Drug Administration (FDA) have required black box warnings regarding serious psychiatric side effects for Varenicline and Bupropion. The warnings refer to suicidal/self injurious behaviors as well as depression [14]. Some epidemiological studies reported that the increased risk for suicidal/self injurious behaviors and depression are due to smoking cessation medications and are independent of quitting [14]. It is unknown how using cessation medications can influence the risk of suicide among schizophrenia patients. Therefore, the specific aims of this study will be:

Objective I: To compare different pharmacotherapies in smoking cessation (NRT, Bupropion, Varenicline, or combination therapy) and to examine which medication could lead to a higher smoking abstinence rate for both short (12 weeks + 4 weeks) and long term (one year) among schizophrenic patients. We will also identify other predictors of successful smoking cessation.

Hypothesis: Schizophrenic smokers who were on Varenicline are more likely to quit smoking both in the short and long term as compared to those on NRT, Bupropion SR, or combination therapy.

Objective II: To assess which cessation medication exposure would have lower risks in developing risk factors of cardiovascular diseases: elevated glucose, cholesterol, and blood pressure level among schizophrenic patients.

Hypothesis: Schizophrenic smokers who tried to quit smoking with NRT are less likely to have elevated glucose, cholesterol, and blood pressure level during one year follow up as compared to those who tried to quit with Bupropion SR and Varenicline.

Objective III: To assess which smoking cessation exposure would have lower risks of suicide behaviors or attempts among schizophrenic patients.

Hypothesis: Schizophrenic smokers who tried to quit with NRT are likely to have suicidal behaviors or attempts during 1 year follow up as compared to those on Bupropion SR or Varenicline.

BACKGROUND

Tobacco Smoking

Smoking is a serious public health problem. Tobacco use causes approximately 443,000 premature deaths annually in the United States (US) [1, 2] and 5.4 million worldwide [3]. The annual economic losses to the US society are estimated at $193 billion with $96 billion in direct medical costs [1]. Despite anti-smoking campaigns, there are about 1.3 billion cigarette smokers worldwide and this number is still increasing [15]. As compared to the general population, schizophrenic patients have much higher smoking rates.

Schizophrenia

Schizophrenia is a debilitating mental disorder in the United States. Strauss and colleagues separated schizophrenia symptoms into 3 specific complexes: positive symptoms, negative symptoms, and disorders of relating. For now, it is more common to classify the symptoms dichotomously as positive/negative, or type I/type II schizophrenia [16]. The negative

symptoms of schizophrenia are defined as the absence of normal behaviors and functions, and thus cause emotional dullness, failure of mental activities [16]. On the other hand, hallucinations and delusions are very common examples of positive symptoms. They are the most striking and characteristic features of schizophrenia [1]. People with schizophrenia typically hear voices (auditory hallucinations). The voices may speak directly to the patient, comment on the patient's actions, or discuss the patient among themselves, and this can lead to the development of strange beliefs or delusions [17]. Common symptoms aside from hallucinations and bizarre delusions include disorganized speech and thinking, and it is accompanied by significant social or occupational dysfunction [18]. The clinical performances of schizophrenia are heterogeneous; virtually no two patients present with the same symptoms, moreover, even in the same patient, symptoms can show dramatic change over time [19].

From systematic reviews, the prevalence of schizophrenia is about 0.72% and it often starts in early adult life and becomes chronic [17]. Men have higher prevalence (risk ratio 1.4:1), an earlier age of onset, and also tend to experience a more serious form of the illness with more negative symptoms, less chance of a full recovery, and a generally worse outcome [17]. Schizophrenia is devastating for both sufferers and their careers. Patients are likely to be unemployed or fail to fulfill their original potential [1]. Genetic (positive family history), environmental factors (migrant status, and urban life), and drug abuse (cocaine or amphetamines) are some possible causes of schizophrenia [17].

Anxiety, depression, and substance abuse are common accompaniments of the schizophrenia condition. Anxiety includes panic disorder, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), generalized anxiety disorder, and social anxiety disorder [19]. Prevalence rates are 37-45% for panic disorder, approximately 13-36% for concurrent

social anxiety disorder, and roughly 10–20% meet full diagnostic criteria for obsessive–compulsive disorder in schizophrenia patients [20]. It is estimated that comorbid depression occurs in 50% of patients, and 47% of patients also have a lifetime diagnosis of comorbid substance abuse [19]. Schizophrenic patients with substance abuse problems are associated with several serious consequences, which include: (1) more positive symptoms, (2) relapse of psychosis, (3) heightened risk of suicide and violence, (4) more medical comorbidities, and (5) greater propensity to anti-psychotic related side effects [19]. Clinical and epidemiological studies estimate that between 40–60% of patients with schizophrenia abuse alcohol or illicit drugs [21]. Another common substance abuse among schizophrenic patients is tobacco smoking; according to previous studies, 72% - 90% of patients with schizophrenia smoke cigarettes, compared with 23% in the general population [4]. The high prevalence can be possibly due to the self-medication effect of tobacco [22]. Tobacco may be used to alleviate some of the symptoms in schizophrenia and the side-effects of antipsychotic medications [23]. People with schizophrenia display attentional, short-term memory, and executive control deficits that limit everyday functioning [24]. The possibility that schizophrenic patients self-medicate such deficits is supported by findings from healthy subjects and laboratory animals: nicotine and other nicotinic acetylcholine receptor (nAChR) agonists enhance sensory, alerting, attentional processes [24]. Quitting smoking may worsen their psychiatric symptoms, therefore, these patients cannot and do not want to quit their tobacco use [25]. For general population adults, according to Lenert et al. [26], the vast majority of smokers try to quit without professional help (80%); but only about 10% of them succeed. Previous studies have shown that schizophrenic patients tend to be heavy smokers [5], to have much lower smoking cessation rates and higher nicotine dependence level [6, 7] compared to general population. Therefore, achieving quitting

smoking might be a too high standard for them. If smoking cessation couldn't be reached, then smoking reduction should be the next goal to consider. Smoking reduction is defined as to cut down $\geqq$50% of cigarette smoked from baseline [27].

People with schizophrenia die on average 10 years earlier than people in the general population, and age-adjusted rates of death because of cardiac and pulmonary disease are significantly elevated in this population, suggesting that tobacco use is an important cause of the excess mortality observed in schizophrenia [28]. Cardiovascular disease is the leading cause of death from smoking, with rates higher than cancer and respiratory disease. Conversely, smoking is one of six major modifiable risk factors for cardiovascular disease [29]. According to the Systemic Coronary Risk Evaluation (SCORE) project, the 10-year fatal cardiovascular risk is approximately doubled for smokers vs. nonsmokers for any given age [29].

Although individuals with schizophrenia constitute approximately only less than 1% of the general population as mentioned earlier, the medical and economic burden of cigarette smoking among mentally ill patients is enormous [6]. Thus, there is great public health significance in developing safe and effective tobacco cessation pharmacotherapies in this population.

Smoking Cessation Interventions

Smoking cessation is highly recommended by public health department of various organizations and several smoking intervention strategies are available for smokers. During the 1990s, a variety of pharmaceutical cessation aids became available, which include nicotine replacement therapy (NRT) and the antidepressant Bupropion SR [8]. Even more recently, Varenicline was approved as an aid to smoking cessation [9].

Two-milligram prescription-only nicotine gum was first introduced in the United States in February 1984. Prescription-only nicotine patches were introduced in 1992, followed by different nicotine doses and medication formulations including 4-mg nicotine gum (1992), a nasal spray (1996), inhaler (1997), and lozenge (2003) [30]. Nicotine medications appear to help smokers in quitting by providing relief from nicotine withdrawal symptoms typically experienced during the first few days and weeks of abstinence from tobacco. In 1996, the U.S. FDA made nicotine patches and gum available over the counter (OTC) in an effort to increase access to these medications, and for now, nicotine lozenge is available OTC as well [30]. Of the various nicotine medications sold, the nicotine gum and nicotine patch are the most frequently used stop-smoking medications. Their FDA suggested dosage regimens are:

Nicotine gum is available in 2-mg and 4-mg (per piece) doses. The 2-mg gum is recommended for patients smoking less than 25 cigarettes per day; the 4-mg gum is recommended for patients smoking more than that. Smokers should use at least one piece every 1 to 2 hours for the first 6 weeks; the gum should be used for up to 12 weeks with no more than 24 pieces to be used per day [31].

Nicotine patch, treatment of 8 weeks or less has been shown to be as efficacious as longer treatment periods [31]. For the first 4 weeks, it is suggested to use the 21mg/24-hour patch, followed by 2 weeks 14mg/24-hour patch, and then 2 weeks 7mg/24-hour patch [31]. The recommended dosing regimens are different among each smoker depends on the number of cigarettes. National survey data reveal that approximately 40% of smokers indicate that they have used some form of nicotine medication in the past [30].

Bupropion is a weak catecholamine reuptake inhibitor and also a potent noncompetitive ion channel site antagonist at the nicotinic acetylcholine receptor (nAChR) [6]. Manufactured by

GlaxoSmithKline, it was originally approved by the FDA for treating patients with depression under brand name Wellbutrin in 1996 [32]. The manufacture received many reports regarding its side effects on reducing cravings with cigarettes smoking after the drug entered the market. Therefore, they decided to use the same medication for patients who want to quit smoking. The sustained-release (SR) formulation of Bupropion was approved for smoking cessation in the United States in the following year, 1997, under the trade name Zyban® [6]. The FDA suggested dosage regimen is: patients should start Bupropion SR 1–2 weeks before they quit smoking with a dose of 150 mg every morning for 3 days, then increase to 150 mg twice daily. Dosage should not exceed 300 mg per day. Dosing at 150 mg twice daily should continue for 7–12 weeks. For long-term therapy, use of Bupropion SR 150 mg for up to 6 months post-quit is considered [31].

The new drug therapy Varenicline was approved by both the US FDA and the European Medicines Agency of the EU in 2006 and subsequently, it has been approved in over 80 other countries [9]. Varenicline is an orally administered small molecule with partial agonist activity at the α4β2 nicotinic acetylcholine receptor [9]. The FDA suggested dosage regimen is: start Varenicline 1 week before the quit date at 0.5 mg once daily for 3 days, followed by 0.5 mg twice daily for 4 days, followed by 1 mg twice daily for 3 months. Varenicline is approved for a maintenance indication for up to 6 months (patient should be instructed to quit smoking on day 8, when dosage is increased to 1 mg twice daily) [31].

In addition to pharmacologic methods in helping smokers quit, behavioral methods are also available, for example, consultations from healthcare providers, educational programs, and mass media interventions [33]. In this study we will mainly focus on the pharmacologic methods.

Though quitting smoking is highly recommended, the mental health system has been reluctant to identify and treat tobacco dependence. This fact may be linked to the belief on the

part of mental health professionals that they do not have the skills to provide smoking treatment options to their patients, the failure to understand that mental health patients can succeed in quitting smoking, as well as reimbursement concerns [34]. Another possible reason for explaining the hesitation of treating tobacco dependence is the perception that schizophrenic smokers might exacerbate their symptoms during nicotine withdrawal and thus healthcare providers are not willing to take such a risk.

Medications that might affect smoking

In addition to the medications that are approved by FDA and listed above, some other medications are thought to increase the rates of quitting smoking, like anti-depressants. Other antidepressants including doxepin, tryptophan, venlafaxine, and alternative therapies such as St. John's wort have been tested in some clinical trials [35]. The most common rationale for using antidepressants for smoking cessation is that (a) abstinence increases depression, (b) depression increases relapse, and (c) depression can be prevented by antidepressants [36]. Following Bupropion, the second most commonly tested medication for smoking cessation is the tricyclic antidepressant Nortriptyline. It is sometimes prescribed when first-line treatments have been unsuccessful, and is actually licensed for smoking cessation in New Zealand. The recommended regimen is 10 to 28 days of titration before the quit attempt, followed by a 12-week dose of 75 to 100 mg daily [35]. An article review included 6 placebo-controlled trials with the efficacy of Nortriptyline for smoking cessation and the results showed it doubled quit rates (OR=2.1) [36]. No other antidepressants are currently licensed for use as smoking cessation aids.

Anxiolytics like Buspirone have also been proposed as treatments. Anxiety is a symptom of nicotine withdrawal, and smoking may decrease anxiety. Anxiolytics may therefore aid cessation by abating a withdrawal symptom or by replacing the reinforcing effects of nicotine.

Buspirone is a non-benzodiazepine anxiolytic with effects on serotonin neurotransmission. Doses used in smoking cessation trials have ranged from a maximum of 30mg/day to 60 mg/day, over a period of nine to thirteen weeks. There is no consistent evidence that Buspirone could aid smokers in quitting, but the available evidence does not rule out a possible effect [37].

Clonidine, a FDA approved medication for treating hypertension has also demonstrated efficacy as an aid to smoking cessation. It is available in tablets for oral administration and as a transdermal patch [38]. A Cochrane review article focused on 6 clinical trials using either oral tablet (0.15 - 0.45 mg/day) or transdermal patch (0.1 to 0.3 mg/day). Pooled results demonstrated an approximate doubling rate of abstinence after 12 weeks of follow-up compared with placebo (OR, 1.89; 95% CI, 1.30 to 2.74). However, Clonidine did not improve the long term quit rates [39].

Naltrexone, a primary mu-opioid receptor antagonist that is currently FDA approved for the treatment of opioid and alcohol dependencies. It occupies the μ-opioid receptors, which putatively diminishes the activation of mesolimbic dopamine and therefore may reduce craving for nicotine [40]. The rationale for the use of Naltrexone in smoking cessation comes from animal studies showing an association between opioids and nicotine. However, the results of studies among smoking behavior in humans have been mixed. Some more recent studies showed it improved quit rates in women but not in men [41]. Another medication, Rimonabant, a selective type 1 cannabinoid receptor antagonist, also showed its potential in improving smoking cessation rates. A review concluded that Rimonabant at 20 mg daily increased the odds of cessation by 1.61 (95% CI 1.12–2.30), although the evidence for maintaining abstinence is inconclusive [42]. Early in 2006, the FDA issued a non approvable letter for the smoking

cessation indication, thus further studies may be required before the FDA will reconsider approval of Rimonabant for smoking cessation [38].

Mecamylamine, a nicotinic receptor channel blocker, has been found to effectively promote cigarette smoking cessation. The rationale for using Mecamylamine to aid smoking cessation is that it is expected to reduce the satisfaction associated with smoking and the urge to smoke [43]. In preclinical rat studies, it has been shown to reduce ethanol self-administration and to reduce cocaine craving in cocaine addicts. Thus, it may be useful for a variety of types of drug addiction [43].

The drugs listed above are all second-line therapies that do not have FDA's approval for smoking cessation but have demonstrated efficacy in some clinical trials. They are recommended for patients who are unresponsive to or unable to tolerate first-line medications.

Medications for Treating Schizophrenia

There are two kinds of antipsychotics: typicals (first generation, or conventional) and atypicals (second generation). The conventional antipsychotics such as haloperidol and chlorpromazine are frequently used as the first line treatment for people with schizophrenia, but about 5-25% of these people show poor response to these treatments [44]. Moreover, adverse effects such as movement disorders (i.e. distressing restlessness or tardive dyskinesia) often make compliance with the first generation of drug treatment problematic [45].

Second generation antipsychotics (SGAs) are believed to be more effective and safer than conventional antipsychotics [46], and they have become the drugs of choice in some countries including the United States in treating schizophrenic patients [47]. Drugs within this class include Clozapine, Risperidone, Olanzapine, Quetiapine, Amisulpride, Aripiprazole, Sertindole, Ziprasidone, and Zotepine [47]. Clozapine, however, is used more commonly for patients whose

symptoms are predominantly refractory [46]. There are substantial concerns about the metabolic side effects of SGAs such as changes in body weight, glucose utilization, or lipid status [47]. For some physicians these side effects are the most important as they might predispose patients to type 2 diabetes mellitus and cardiovascular disease [47].

Smoking cessation and the change in mental state of schizophrenic patients

There are several available measures for the mental state such as brief psychiatric rating scale (BPRS), Calgary Depression Scale for Schizophrenia (CDSS), or Hamilton Depression Rating Scale (HAM-D). The Positive and Negative Syndrome Scale (PANSS) is another one of the most widely used methods for standardized measurement of schizophrenic core symptoms [48].

PANSS is based originally on the BPRS and the Psychopathology Rating Schedule. It consists of 7 positive symptom items, 7 negative symptom items, and 16 general psychopathology items like anxiety, tension, depression, or poor attention. All 30 PANSS items are rated on a 7-point symptom severity scale, ranking from 1 (absent) to 7 (extremely severe) [48].

Gaps in research

(1) Abstinence comparison between cessation medications

Studies that have been conducted among schizophrenic smokers were with very small sample sizes and all were in a rigorously controlled RCT pattern [28, 49-55]. No head to head comparison trials between cessation medications have been conducted and thus it is unclear which medication is more effective among this population.

(2) Beneficial effect of quitting - Cardiovascular diseases

From previous research, there is a relationship between the degree of exposure to smoking and the level of risk of having cardiovascular diseases. A meta-analysis of five large, prospective, epidemiologic studies found that the relative risk (RR) of heart disease from smoking 1 cigarette/day was 1.39 (95% confidence interval: 1.18 - 1.64, $p < 0.001$, reference= nonsmokers) increasing to 1.78 in subjects who smoked 20 cigarettes/day [29]. Risk factors for cardiovascular diseases include diabetes, hyperlipidemia, and hypertension. Although smoking cessation is associated with substantial health benefits, weight gain after quitting is commonly cited [10]. Because of diseases that could result from the weight gain, this is a great concern. Studies report a higher incidence of diabetes or hypertension among smokers that quit compared to those who continue with the smoking habit [11, 12]. The schizophrenic patient population already has higher risks of diabetes/hyperlipidemia/hypertension because of the side effects of the atypical antipsychotics regimen. The combined weight gain from smoking cessation could worsen the risk. Furthermore, NRT has been shown to reduce sensitivity to insulin which may aggravate or precipitate diabetes [56] and recent reviews actually showed an increasing risk of cardiovascular disease for those who take Varenicline. It is unclear how using different smoking cessation regimens can modify these risks for schizophrenic patients as no studies have been conducted among this specific population. While physicians or healthcare professionals are trying to convey the quitting smoking message to schizophrenic smokers, literature with the benefits of quitting while comparing the risks among different cessation medications will be helpful to support their suggestions.

(3) Stability in mental state after quitting

As mentioned above, PANSS is the most widely used method for standardized measurement of schizophrenic core symptoms. However, the scale is not available in GE data; we thus used another approach to measure the stability of mental state.

The U.S. Food and Drug Administration (FDA) have required black box warnings for patients regarding serious psychiatric side effects for two pharmacological treatments, Varenicline and Bupropion. The warnings refer to suicidal/self injurious behaviors and also depression [14]. Some epidemiological studies reported the increased risk for suicidal/self injurious behaviors and depression are due to smoking cessation medications and are independent of quitting [14]. The lifetime risk of suicide in schizophrenic patients is much higher than that in the general population, and suicide is actually the leading cause of premature death among patients with schizophrenia [13]. No studies have been conducted among this specific minority population examining if risks of suicide are higher for those taking Bupropion SR and Varenicline. This information is critical for healthcare professionals as they may need to monitor their patients more closely during the process of quitting.

Statement of Problem

Schizophrenic patients have higher smoking rates and lower cessation rates as compared to those without schizophrenia. This minority group also dies on average 10 years earlier than the overall population partially due to cardiac and pulmonary disease from tobacco smoking [28]. Although individuals with schizophrenia constitute approximately less than 1% of the general population, the medical and economic burden of smoking among mentally ill patients is enormous [6]. With several available smoking cessation regimens, studies that examine which cessation medication is more effective in reaching abstinence both in the short and long term specifically in this population are lacking. The benefits of quitting among schizophrenic patients

should be carefully evaluated as tobacco may be used to alleviate some of the schizophrenic symptoms [23]. It is also important to evaluate how different smoking cessation medications can interact with the antipsychotic regimens used by these patients and how that affects the risks of developing cardiovascular disease risk factors: elevated glucose, cholesterol and blood pressure. In addition, literature reports an increase in suicidal behaviors/attempts when using some cessation medications in the general population. Suicide is already the leading preventable cause of death in schizophrenia [13], thus comparing the risk of suicidal behaviors/attempts among schizophrenic patients using different cessation regimens is greatly needed.

PROJECT SUMMARY LITERATURE REVIEW AND THEORY

A comprehensive literature search was conducted in the bibliographic databases Qvid Medline, Pubmed, Embase (Ovid), and Psycinfo (Ovid) using a combination of keywords. Those key words can be found in Appendix A. From the search, no retrospective cohort studies have been done comparing smoking cessation products among schizophrenic smokers. Though quite a few RCTs have been conducted for smoking cessation among the general population, very little RCTs popped out for schizophrenic smokers. While searching, there was a Cochrane review published in 2010 with similar searching terms. The review only included studies with Bupropion and NRT as there were no articles for Varenicline clinical trials available at the time it was conducted. Thus, in order to fill that gap, studies with clinical trials that got published after 2010 were first searched, then the trials that were included in the Cochrane review were then combined together.

Aside from the cessation medication itself, we did not find any studies that examined other predictors of successful smoking cessation, and for the RCTs we found, they usually had

different smoking abstinence definitions with different follow up periods. The ideal definition of abstinence should be based on the "Russel Standard – at least 6 months after starting the medication", a common standard for outcome criteria in smoking cessation trials [57]. However, trials among this specific mental disorder group were relatively short with the definition of abstinence usually shorter than 6 months. The following literature results are all based on RCT evidences. The inclusion criteria, participants' characteristics, definitions of abstinence, study outcomes and other information of the RCTs are summarized in Appendix B and Appendix C.

Smoking Abstinence for Nicotine Replacement Therapy

Chou et al. published a RCT in 2004 [49]. They enrolled schizophrenic patients aged above 18 and smoked ≥15 cigarettes/day for at least 1 year. The exclusion criteria were: (1) use of NRT within 6 months before study enrollment, (2) current use of other smoking cessation treatments, (3) regular use of any non-cigarette tobacco product, and (4) with serious or unstable cardiac, hypertensive, renal, pulmonary, endocrine, or neurological disorders. A total of 68 individuals were recruited for the study. Twenty-six subjects were randomly assigned to the nicotine-patch group and 42 subjects were assigned to the control group. None of the subjects dropped out during the study. The NRT protocol was an 8-week 14mg patch per day during weeks 1-6, and 7mg per day during weeks 7–8. The 7-day point-prevalence rate of abstinence was measured at the 8th week right after the treatment finished and 3-month follow-up. Point-prevalence abstinence refers to the percentage of people who were not smoking during the previous 7 days (self-reported cigarette use and verified with a CO < 10 ppm). The authors found that smoking abstinence rate in the NRT group was 26.9% (7 out of 26) at 8th week and 26.9% (7 out of 26) at 3-month follow up. They did not report the abstinence rate for those in placebo

group at the 8th week but it was 0% with the 3 month follow up. In this study, side effects of the nicotine patch or changes in the clinical mental state were not reported as well.

Another RCT for transdermal nicotine patch assessed different doses of nicotine on the effect of abstinence at two public psychiatric hospitals in Taiwan from 06/2005 to 12/2006 [50]. Participants were randomly assigned to either the high dose (31.2mg for the first 4 weeks and 20.8mg for 4 weeks) or the low dose (20.8mg for 8 weeks) nicotine patch group. They had a total of 92 subjects completed the trial in each of the treatment group. The authors examined the abstinence (7-day point prevalence) at the end of trial at the 8th week. They found no differences ($p=0.174$) between the two groups: 4/92 in the low dose and 1/92 in the high dose reached abstinence. However, in this high dose nicotine patch protocol, it exceeded the dose that was recommended by the FDA (21mg/24-hour patch for the first 4 weeks, 14mg/24-hour for the following 2 weeks, then 7mg/24-hour for 2 weeks) [31]. That can potentially explain why the authors didn't find any differences.

Smoking Abstinence for Bupropion

A pilot trial for Bupropion SR among schizophrenic smokers was published in 2001 by Evins et al. [51]. They included participants at an urban community mental health center who had been on a stable dose of antipsychotic medications for at least 4 weeks, and who reported cigarette use greater than half a pack/day and a desire to quit smoking. All subjects participated in a CBT (cognitive behavioral therapy). The quit smoking group program was designed for patients with schizophrenia and consisted of nine weekly 1-h group sessions co-led by a nurse experienced in smoking cessation counseling and a cognitive behavioral psychologist. Eighteen subjects completed the trial with 9 subjects in each of the group. Both of the groups received the treatment for 3 months with Bupropion SR 150mg/day in the active treatment arm and placebo in the other arm. Bupropion treatment (6/9 subjects, 66%) was associated with significantly greater

reduction in smoking (self-report of a 50% reduction from baseline in cigarettes smoked per day verified by a 30% reduction in expired-air CO) than placebo (1/9 subjects, 11%) during the 3-month active treatment period. Same as the 3-month follow-up period, one subject in the Bupropion group (11%) and no subjects in the placebo group achieved sustained tobacco abstinence for the 6-month trial. Compared to placebo, Bupropion treatment was associated with improvement in negative symptoms and greater stability of psychotic and depressive symptoms. Furthermore, there were no serious adverse events reported for participants on Bupropion.

The same research group, Evins et al. [28] conducted another clinical trial from 1999 to 2003 with a larger population, they recruited schizophrenic patients who smoked > 10 cigarettes/day and also had a desire to quit from 5 urban community mental health centers in Massachusetts. They randomly assigned them to receive either Bupropion SR 300 mg/day or identical placebo for 12 weeks. CBT intervention was delivered as well for both of the groups. Fifty-three adults, 25 on Bupropion and 28 on placebo, completed at least one post-baseline assessment. They also defined abstinence with the 7-day point prevalence. The authors found that subjects in the Bupropion group were significantly more likely to be abstinent 4 weeks after the quit date (36% [9/25] vs. 7% [2/28], P = 0.016) and at the end of intervention (week 12) (16% [4/25] vs. 0%, P = 0.043). As far as the mental clinical symptoms are concerned, there was a decreasing trend from baseline to week 12 for Bupropion for all the Scale for the Assessment of Negative Symptoms (SANS), Hamilton Depression Rating Scale, and PANSS total scores. Thus, there was no worsening of the clinical symptoms but an improvement on the other hand.

Another group of researchers George et al. published a study in 2002 [52]. They conducted the RCT in an outpatient smoking research clinic of The Connecticut Mental Health Center. Participants were required to be clinically stable on the psychotic symptoms at baseline,

to have a Fagerstrom Test for Nicotine Dependence (FTND) score at least 5, an expired CO level at least 10 ppm, and a strong desire to quit smoking. Eligible subjects were randomly assigned to either placebo or Bupropion SR (300mg/day for the first 3 days, then 300mg b.i.d. until the end of week 10). The authors assessed abstinence with both short term and long term. For the short-term, they had (1) at the end point of the trial (week 10) 7-day point prevalence abstinence, and (2) abstinence during the last 4 weeks (week 7-10). For the long term, they had the follow up at 6^{th} month. In the Bupropion group, 8/16 had achieved quitting compared with 2/16 in the placebo ($p<0.05$) at the 10^{th} week. For the last 4 weeks continuous abstinence, 6/16 in Bupropion vs. 1/16 in placebo reached the goal ($p<0.05$). When the authors examined the long term effect, however, no significant differences were observed between the two treatment groups. For clinical mental state, positive schizophrenia symptoms were not altered by Bupropion SR, but negative symptoms were significantly reduced (around 15%). Major side effects that were reported for Bupropion included dry mouth, gastrointestinal symptoms, headache, and insomnia.

The majority of Bupropion SR RCTs showed positive effect toward smoking cessation among schizophrenic smokers. However, another clinical trial that got published later had a different abstinence result [53]. Bloch et al. recruited patients from two community mental health centers and two ambulatory clinics in northern Israel. Subjects were referred by their treatment team and were judged by their psychiatrists to be clinically stable and had a stable dose of anti-psychotic drugs for at least one month prior to the start date. The study was a 16-week, prospective, double blind, placebo controlled study. Subjects were randomly allocated to either the treatment group (Bupropion SR 300 mg/day + CBT) or control group (placebo + CBT) at a rate of 2:1. Initial dose was 150 mg/day for 3 days and then 300 mg/day. Study medication was for 14 weeks following a 2-week stabilization period. All subjects participated in a 14-week, 15-

session group CBT. The CBT program emphasized education, motivation, encouragement, problem-solving strategies, coping with triggers, behavioral tasks and cognitive reconstruction. Twenty one participants in the treatment group and eleven in the placebo completed the trial. Bloch et al. found that at the end of treatment (14 weeks), both groups of subjects demonstrated significant reductions in smoking behavior due to CBT, however, subjects receiving Bupropion did not show significant differences in smoking behavior when compared to placebo.

Smoking Abstinence for Varenicline

Varenicline RCTs among schizophrenic smokers are scarce because it is the most recent FDA approved medication for smoking cessation. A double blind randomized pilot study was conducted by Weiner et al. in 2011 [54]. The enrollment criteria for participants included: had schizophrenia or schizoaffective disorder (DSM-IV TR) over 3 years, smoked ≥10 cigarettes/day, had been smokers for one year and scored a total of at least "4" on the Fagerstrom Test for nicotine dependency. Participants received either Varenicline (1 mg twice daily) or placebo for 12 weeks and all participants received individual smoking cessation counseling. Nine subjects were randomized (n=4 for Varenicline, and n=5 for placebo) and 8 subjects completed (with 4 participants in each group). On the primary outcome measure of smoking cessation (defined as expired CO＜10 at each of the last 4 visits), 3/4 (75%) Varenicline participants achieved sustained abstinence at endpoint and 0/4 of the placebo group were considered abstinent. No subject showed significant exacerbation of psychotic, depressive or other psychiatric symptoms. Overall side effects were low in both groups, though members of the Varenicline group tended to report worsening of constipation (2 vs 0), insomnia (3 vs 1), and nausea (3 vs 1).

After that pilot study, Williams et al. conducted a RCT with a large number of participants at 12 research centers in the United States and Canada from 2008 to 2010 [55]. The

study comprised a 2-week screening period, 12-week treatment period, and 12-week post-treatment follow-up period. Participants all smoked ≥15 cigarettes/day, had no period of smoking abstinence over 3 months during the previous year, had a motivation to quit, and were mentally stable with a total PANSS score of less than 70. Eighty-four participants received Varenicline and 43 received placebo. Varenicline dosing began with a 1-week titration period with one 0.5mg/day on days 1-3, followed by two 0.5mg/day for the next 4 days. From week 2 to the week 12 visit, patients took 1mg/day. They defined smoking abstinence as not smoking in the past 7 days at week 12 and 24, verified by carbon monoxide level. At 12 weeks (end of treatment), 16/84 Varenicline treated patients (19%) met the cessation criteria versus 2/43 (4.7%) for placebo (p=0.046). At 24 weeks, 10/84 (11.9%) Varenicline treated and 1/43 (2.3%) placebo treated patients achieved the cessation criteria (p=0.09). Total, positive, and negative PANSS scores remained stable or slightly decreased from baseline to week 12 and 24 in both groups, indicating no worsening of psychotic symptoms. Total adverse event rates were similar as well between the two groups, but nausea, headache, and vomiting were being reported more common in the Varenicline group.

Beneficial effect of quitting – cardiovascular diseases' risk factors

Cardiovascular disease is an important cause of morbidity and mortality among tobacco users. The long-term cardiovascular benefits of smoking cessation are well established [29, 58]. Many pathophysiological changes caused by smoking can be reversed or improved by smoking cessation. A systematic review in patients with CHD showed that smoking cessation reduced the relative risk of death by 36% and risk of re-infarction by 32% compared with continuing smokers [29].

Cardiovascular disease is a long term outcome. Based on the National Cholesterol Education Program (NCEP), some identified risk factors for developing cardiovascular disease include: (1) elevated fasting glucose (≧110 mg/dl), (2) elevated triglycerides (≧150 mg/dl), and (3) blood pressure level (≧130/ ≧85 mm Hg) [59]. These factors can be assessed in a short term study.

For NRT

Chronic smokers who quit with the assistance of nicotine chewing gum demonstrated a significant reduction in LDL (5.6%) and a non-significant increase in HDL (3.4%) [29]. Not limited to abstinent from smoking, smokers who reduced cigarettes also had similar results. Those who were interested in quitting were randomized to NRT or placebo. Successful non-abstinent reducers showed significant improvements in a number of biomarkers (e.g., hemoglobin, red blood cell and white blood cell counts, lipids, blood pressure, heart rate, and respiratory symptoms) [29].

For Bupropion SR

Fewer studies were conducted among Bupropion SR with the clinical changes. After 6–7 weeks of receiving Bupropion SR, HDL levels increased while LDL levels remained unchanged. According to a review of Bupropion SR for smoking cessation, occasional cases of hypertension requiring acute treatment have been reported; however, no statistically significant mean changes for both systolic and diastolic blood pressure have been noted during treatment with the general population of smokers or those with pre-existing stable cardiovascular disease [60].

For Varenicline

Williams et al. conducted a double-blind, multi-center RCT among 377 eligible adult smokers (18-75 years old, who smoked an average of ≥10 cigarettes/day) between October 2003

and March 2005. They randomly assigned participants to either Varenicline (1 mg twice daily) or placebo for 52 weeks. Two hundred and fifty one were in the active treatment arm and 126 were with placebo. Subjects made weekly clinic visits until week 8, and then every 4 weeks until week 52. At each visit, adverse events and vital signs like blood pressure were documented. The final results showed that median changes in blood pressure from baseline to last observation, as well as mean changes from baseline to each visit, were small and indicated no differences between treatment groups [61].

Another multi-center, double blind RCT showed similar findings among patients with pre-existing stable cardiovascular disease: 714 smokers were recruited to examine efficacy and safety of Varenicline vs. placebo for smoking cessation. Participants received Varenicline (1 mg twice daily) or placebo, along with smoking-cessation counseling, for 12 weeks. There were no differences in blood pressure level between the two groups at week 1, and patients were asked to come back for physical exams like blood pressure or blood tests at week 12. Regardless of quitting smoking, two groups did not differ in the change of blood pressure from baseline to the end of drug treatment [62].

Even though smoking cessation is associated with substantial health benefits, weight gain after quitting is commonly cited, especially among women, as a primary reason for not trying to quit and for relapsing after cessation [10]. In the U.S., it is estimated that 80% of people who quit smoking gain weight [11]. The average weight gain in people who sustained quitting for eight years was about 9kg, with 42% of people gaining over 10kg. This weight gain can have health consequences, with the incidence of diabetes being higher in smokers that quit smoking than those who continue with it [11]. Yeh et al. [63] found that in the first 3 years of follow-up, compared with non-smokers, the hazard ratios of diabetes among former smokers, new quitters,

and continuing smokers were 1.22 (95% CI: 0.99 – 1.50), 1.73 (95% CI: 1.19 – 2.53), and 1.31 (95% CI: 1.04 – 1.65), respectively. This indicates that smoking cessation leads to a higher short-term diabetes risk. Furthermore, in other studies, NRT has shown to reduce sensitivity to insulin and may aggravate or precipitate diabetes [56].

In addition to diabetes, the risk of hypertension may increase after quitting smoking. Janzon et al. [12] included a total of 2,381 female never smokers and 1,550 female smokers in a 9-year follow up study. At the end, 388 of the 1,550 smokers had quit smoking. They found that after 9-years of follow up, mean weight gain was 7.6 ± 6.1, 3.2 ± 5.8 and 3.7 ± 5.2 kg, respectively, in quitters, continuing smokers and never smokers ($P < 0.001$). In women without blood pressure medication treatment, mean SBP increase was 20.9 ± 16.8, 19.1 ± 15.8 and 16.1 ± 16.3 mmHg, respectively ($P < 0.001$). Mean DBP increase was 6.2 ± 8.7, 5.7 ± 9.3 and 3.1 ± 8.0 mmHg, respectively ($P < 0.001$) (quitters, continuing smokers and never smokers). After adjustments for potential confounders, the differences in SBP and DBP increase were attenuated, but remained significant. Incidence of hypertension (≧ 160/95 mmHg or anti-hypertension treatment) was significantly higher in quitters (adjusted OR: 1.8, 95% CI: 1.4–2.5), and continuing smokers (OR: 1.3; CI: 1.07–1.6) when compared with never smokers. Another study conducted by Terace et al. [64] also reported a similar finding. They found more quitters (35%) became hypertensive than non quitters (27%, $p<0.01$) after 7 years of follow up, although the two groups (quitters and non quitters) had similar blood pressure levels at baseline. The increased blood pressure finding or the excess incidence of hypertension in quitters might be due to the effect of weight gain after cessation.

For schizophrenic patients, this would be a bigger concern because the antipsychotic medications they are taking increases their risk of metabolic syndromes. Second generation

antipsychotics (SGAs) have become the drugs of choice for treating schizophrenic patients in many countries including the United States [47] because they are believed to be more effective and safer than conventional antipsychotics [46]. With the weight gain from smoking cessation and SGAs combined, the risks of quitting smoking specifically among schizophrenic patients have to be evaluated. Furthermore, Bupropion has been shown to inhibit enzyme CYP2D6 and would reduce the clearance of drugs metabolized by it (e.g., antipsychotics or tricyclic antidepressants) [28]. Therefore, risks of developing metabolic side effects would be even higher for patients receiving Bupropion.

Aside from that, cessation medications that receive priority review have limited safety data at the time of approval. Many studies for Varenicline before 2010 showed that there were very few side effects and no clinically significant drug–drug interactions were observed [65]. However, some studies and reviews after 2010 actually showed Varenicline increases the chances of developing cardiovascular diseases. A review and meta-analysis [58] analyzed data from 14 double blind randomized controlled trials involving 8,216 participants. The trials ranged in duration from 7 to 52 weeks. Varenicline was associated with a significantly increased risk of serious adverse cardiovascular events compared with placebo (1.06% [52/4908] in Varenicline vs. 0.82% [27/3308] in placebo group; OR=1.72, 95% CI= 1.09–2.71). A report even showed that a 30-year old smoker without previous history of coronary artery disease developed acute thrombotic occlusion and acute coronary syndrome after Varenicline exposure [66]. The product label was subsequently updated in December, 2012, according to FDA's request: "Post marketing reports of myocardial infarction and cerebrovascular accidents including ischemic and hemorrhagic events have been reported in patients taking Varenicline [58]."

Studies have examined the effect of quitting in preventing new onset of cardiovascular diseases among general population and not specifically among schizophrenic smokers. The benefits of quitting among schizophrenic patients should be carefully evaluated as tobacco may be used to alleviate some of the schizophrenic symptoms. There is also a need to evaluate how different smoking cessation strategies can modify these risks among schizophrenic patients given the medication regimens they already take.

Stability in mental state after cessation medication exposure

Suicide is the leading cause of premature death among patients with schizophrenia. Overall, patients with schizophrenia have approximately a 50% lifetime risk for suicide attempts and a 9-13% lifetime risk for completed suicide. In comparison, the lifetime risk for suicide in the general population of the United States is approximately 1% [13]. Most of the completed suicides appear to occur within the first 10 years after illness onset and 50% occur within the first 2 years; however, the risk of suicidal behaviors is lifelong [67].

Many of the important risk factors for suicide in schizophrenia were similar to those in the general population, including being young, male, and with a high level of education, mood disorder, previous suicide attempts, and drug misuse [68, 69]. There are, however, other risk factors that are specific to the disorder. A systematic review with 29 eligible studies identified some of predictors: previous depressive disorders (OR=3.03, 95% CI: 2.06 - 4.46), previous suicide attempts (OR=4.09, 95% CI= 2.79 - 6.01), drug misuse (OR=3.21, 95% CI= 1.99 - 5.17), agitation or motor restlessness (OR=2.61, 95% CI:1.54 - 4.41), fear of mental disintegration (OR=12.1, 95% CI=1.89 - 81.3), poor adherence to treatment (OR=3.75, 95% CI= 2.20 - 6.37) and recent loss (OR=4.03, 95% CI= 1.37 - 11.8). Reduced risk was associated with

hallucinations (OR=0.50, 95% CI= 0.35 - 0.71) [68] and adherence to antipsychotic treatments [69].

Smoking, smoking cessation and cessation medications have shown to be associated with suicide in the general population. The relationships will be described as follows.

The most plausible explanations for smoking and the association of suicide are that smokers have preexisting conditions and smoking decreases serotonin and monoamine oxidase levels. The explanations stated above would increase the risk of suicide [70].

Quitting smoking may (1) lead to major depression in some smokers and (2) result in a withdrawal syndrome that includes worsened mood and other behaviors that would increase the risk of suicide. Many studies have found that negative affect symptoms are the most common symptoms of tobacco withdrawal. A study showed that among 304 women who tried to stop smoking, 21 (7%) reported suicidal ideation during the 6 month post-cessation. Although this study did not have a control group, the rate of suicidal ideation in this study is substantially higher compared to the epidemiological studies of smokers not trying to quit [70].

For NRT, the association with suicide was examined in the Lung Health Study, which randomly assigned smokers to nicotine gum or no medication (not schizophrenic patients) [70]. Over the 5 years of the study, the incidence of suicides was not greater in the nicotine gum vs. control group. If anything, suicides appeared to be less common with gum; i.e., 2/3923 or 0.05% in the nicotine gum group vs. 5/1964 or 0.25% in the control group [70].

Varenicline and Bupropion inhibit the craving to smoke through influencing the dopamine system, which regulates cognition, mood, and behavior. The two medications have been associated with “changes in behavior, agitation, depressed mood, suicidal ideation, and attempted and completed suicide” in patients who had no psychiatric history and were not taking

psychotropics. On the other hand, nicotine replacement products have no such reported associations. Gunnell and colleagues reported the first retrospective cohort study to examine suicidal thoughts and behaviors after exposure to smoking cessation products. They assessed 80,660 men and women aged 18-95 who were prescribed a new course of a smoking cessation product between 2006 and 2008. They found no association between Varenicline or Bupropion and fatal or non-fatal self harm. However, patients experiencing severe adverse events may have discontinued the prescription before it was finished [71].

Since the approval of Varenicline in 2006, there have been reports suggesting that use of Varenicline for smoking cessation in patients with psychiatric disorders may be associated with new-onset depressed mood, suicidal ideation, and emotional and behavioral changes just within days to weeks of exposure. Based on progress in its review of the adverse event reports, the FDA issued a Public Health Advisory with new safety warnings for Varenicline in February 2008, emphasizing since the time of approval, 491 cases of suicidal ideation, attempts or completed suicides have been reported. Thus, there is a need for screening for preexisting psychiatric illness before use and the importance of monitoring/reporting of mood or behavior changes [72]. Many of these occurred while using Varenicline and continued smoking, suggesting they cannot be attributed to nicotine withdrawal. The US Veterans Association released a similar report in 2008, citing 32 instances of suicide among 147,718 Varenicline prescriptions (0.02%). None of these reports provided more detail and neither concluded causality had been established; however, all believed these data indicate further investigation is needed [70].

Based on all the reported side effects, the U.S. FDA has required black box warnings for patients regarding serious psychiatric side effects for two pharmacological treatments, Varenicline and Bupropion. The warnings refer to suicidal/self injurious behaviors and also

depression [14]. Smoker who gets exposed to either of those two medications need to be aware of the psychiatric side effects, regardless of quitting smoking. Since suicide is the leading cause of premature death among schizophrenic patients, the potential risk can be further increased after the cessation exposure and studies examining the risk in this high risk population are greatly needed.

Sum up the literature finding

To sum up, most of the smoking cessation products were shown to be efficacious in smoking abstinence at the end of the trial without jeopardizing their mental state (PANSS). No severe side effects were reported as well. However, most of the clinical trials enrolled schizophrenic smokers with stable clinical mental states at baseline, and the trials were usually being rigorously controlled by the researchers. The results we gathered here could not be generalized to the real world setting. Most of the trials had very little participants; therefore, larger samples are needed to make the evidence more convincing. The trials we found had the smoking abstinence measured mostly at the end of the treatment protocol, usually between week 8 and week 12. However, according to the Russel standard, abstinence should be assessed at least 6 months after starting the medication [57]. In clinical trials, we usually do not have that long follow up period due to the drop out of the participants or the cost of conducting the trial. Furthermore, no head to head comparison between all the smoking cessation products was conducted. Every trial had different enrollment criteria and the definitions of abstinence, thus, it would be difficult to compare the results all together. A way to address all the concerns listed above is through conducting a retrospective cohort study.

Aside from abstinence, no studies have been done among schizophrenic patients examining which cessation medication is associated with lower risks of cardiovascular disease

risk factors or suicide behaviors/attempts. This lacking information is greatly needed for healthcare professionals to better monitor their patients and to convey these messages to schizophrenic patients and/or their relatives while prescribing cessation medication.

MANUSCRIPT 1

Comparative Effectiveness of Smoking Cessation Medications among Schizophrenic Smokers

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INTRODUCTION

Smoking is a serious public health problem. Tobacco use causes approximately 443,000 premature deaths annually in the United States (US) [1, 2] and 5.4 million worldwide [3]. According to previous studies, 72% - 90% of patients with schizophrenia smoke cigarettes, compared with 23% in the general population [4]. The high prevalence can be possibly due to the self-medication effect of tobacco [22]. Tobacco may be used to alleviate some of the symptoms in schizophrenia and the side-effects of antipsychotic medications [23]. Quitting smoking may worsen their psychiatric symptoms, therefore, these patients cannot and do not want to quit their tobacco use [25]. Previous studies have also shown that schizophrenic patients tend to be heavy smokers [5], to have much lower smoking cessation rates and higher nicotine dependence level [6, 7]. Although individuals with schizophrenia constitute approximately only less than 1% of the general population as mentioned earlier, the medical and economic burden of cigarette smoking among mentally ill patients is enormous [6]. Thus, there is great public health significance in developing safe and effective tobacco cessation pharmacotherapies in this population.

Smoking cessation is highly recommended by public health department of various organizations and several smoking intervention strategies are available for smokers. The available pharmacotherapies that are available in the U.S. include nicotine replacement therapy (NRT), Bupropion SR, and the most recent approved one Varenicline [8, 9].

Nicotine medications appear to help smokers in quitting by providing relief from nicotine withdrawal symptoms typically experienced during the first few days and weeks of abstinence from tobacco. Of the various nicotine medications sold, the nicotine gum and nicotine patch are the most frequently used stop-smoking medications.

Nicotine gum is available in 2-mg and 4-mg (per piece) doses. The 2-mg gum is recommended for patients smoking less than 25 cigarettes per day; the 4-mg gum is recommended for patients smoking more than that. Smokers should use at least one piece every 1 to 2 hours for the first 6 weeks [31]. Nicotine patch, treatment of 8 weeks or less has been shown to be as efficacious as longer treatment periods [31]. For the first 4 weeks, it is suggested to use the 21mg/24-hour patch, followed by 2 weeks 14mg/24-hour patch, and then 2 weeks 7mg/24-hour patch [31].

Bupropion is a weak catecholamine reuptake inhibitor and also a potent noncompetitive ion channel site antagonist at the nicotinic acetylcholine receptor (nAChR) [6]. It was originally approved by the FDA for treating patients with depression under brand name Wellbutrin® in 1996 [32]. The manufacture received many reports regarding its side effects on reducing cravings with cigarettes smoking after the drug entered the market. In the following year, 1997, FDA approved the same ingredients but under trade name Zyban® for smoking cessation [6]. The suggested dosage regimen is: patients should start Bupropion SR 1–2 weeks before they quit smoking with a dose of 150 mg every morning for 3 days, then increase to 150 mg twice daily for 7–12 weeks.

The new drug therapy Varenicline was approved by both the US FDA and the European Medicines Agency of the EU in 2006 and subsequently, it has been approved in over 80 other countries [9]. Varenicline is an orally administered small molecule with partial agonist activity at

the α4β2 nicotinic acetylcholine receptor [9]. The FDA suggested dosage regimen is: start Varenicline 1 week before the quit date at 0.5 mg once daily for 3 days, followed by 0.5 mg twice daily for 4 days, followed by 1 mg twice daily for 3 months.

Though quitting smoking is highly recommended, the mental health system has been reluctant to identify and treat tobacco dependence. This fact may be linked to the belief on the part of mental health professionals that they do not have the skills to provide smoking treatment options to their patients, the failure to understand that mental health patients can succeed in quitting smoking, as well as reimbursement concerns [34]. Another possible reason for explaining the hesitation of treating tobacco dependence is the perception that schizophrenic smokers might exacerbate their symptoms during nicotine withdrawal and thus healthcare providers are not willing to take such a risk.

Studies that have been conducted among schizophrenic smokers regarding smoking abstinence were with very small sample sizes and all were in a rigorously controlled RCT pattern [28, 49-55]. No head to head comparison trials between cessation medications have been conducted and thus it is unclear which medication is more effective among this population.

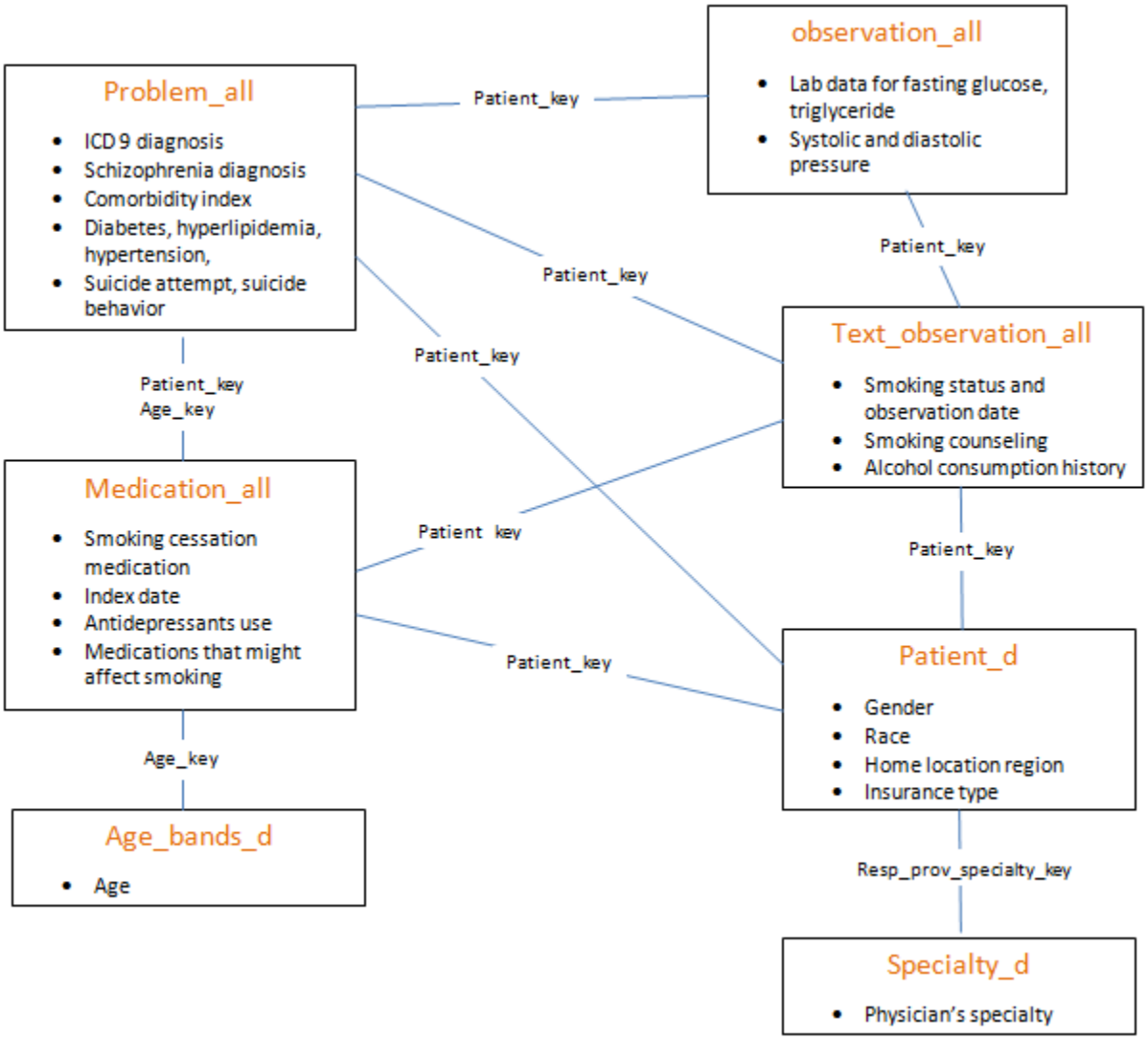
METHODS

Data source

The data used for this study were extracted from the General Electric Centricity Electronic Medical Record (GE EMR) research database. The Centricity EMR database is used by more than 20,000 clinicians and contains longitudinal ambulatory electronic health data for more than 7.4 million patients, including demographic data, vital signs, laboratory orders and results, medication list entries and prescriptions, and diagnoses or problems. A variety of practice types are represented in the database, ranging from solo primary care practitioners to community

clinics, academic medical centers, and large integrated delivery networks [73]. Both medications and prescriptions are documented in the database. Medications may include a broader list of all medications that a patient is taking including over the counter medications, herbal remedies and medications prescribed by a provider that may be out of the EMR network. On the other hand, prescriptions are medications that have been prescribed by the responsible provider of this patient within the EMR. Some forms of NRTs are OTCs and could not be captured in most of the claims data but are available in the GE EMR which makes it an appropriate tool for our data analysis. Moreover, the availability of smoking status information makes it the ideal clinical database to be used. Data are collected centrally and go through a quality-control process to remove invalid values [74]. One study using data in 2005 found the population distribution is very similar between GE EMR and the US population. The proportion of patients aged 18 to 64 years in the GE EMR population is 63%, which is similar to that in the US general population. Furthermore, of the patients in the GE EMR whose race is documented, 79% are white and 15% black, compared with 81% white and 13% black in the US population [74]. GE data set has been widely used in studying smoking, for example, Fox et al. assessed effectiveness of different statins among diabetes mellitus patients with smoking status as one of the covariates [75]. GE data consists of several different files that give different information, for example, (1) problem file has information with ICD9 diagnosis, therefore, comorbitities were obtained here, (2) text observation file has information with patients' alcohol use history, their smoking status and whether they had received smoking counseling, (3) patient_d_file has patients' demographics information like age, gender, race, and geographic region, and (4) medication_all file has information regarding OTCs they took as well as prescriptions they were prescribed. The protocol to linking the different files together is detailed in Figure 1 below.

Figure 1: Linkage between GE data files



Study population

We included patients who were enrolled between 12/13/1995 to 10/31/2011. Patients aged below 18 years old or those who received Wellbutrin® (Bupropion SR) for depression 6 months prior to index date were excluded from this study. From the GE healthcare EMR databases, we identified patients with a diagnosis of schizophrenia or schizoaffective disorder (ICD-9 code 295.00-295.99) [76].

1st objective: To compare different pharmacotherapies in smoking cessation (NRT, Bupropion, Varenicline, or combination therapy) and to examine which medication could lead to a higher smoking abstinence rate for both short and long term among schizophrenic patients. We also identified other predictors of successful smoking cessation among schizophrenic patients.

Hypothesis: Schizophrenic smokers who were on Varenicline would be more likely to quit smoking in both the short and long term as compared to those on NRT, Bupropion SR, or combination therapy.

After identifying the population, we constructed a series of new-user cohort of patients who had newly initiated use of smoking cessation medications. Only the first exposure to each of the smoking cessation medication was examined so we can be sure the quitting is not affected by the previous cessation product they took. There are seven possible treatment regimens for schizophrenic smokers after he/she entered the GE healthcare network: The individual had received (1) NRT only, (2) Bupropion (Zyban) only, (3) Varenicline only, (4) NRT and Bupropion, (5) NRT and Varenicline, (6) Bupropion and Varenicline, and (7) NRT, Bupropion, and Varenicline.

Since smoking cessation medications are usually being prescribed for three months [31], we then used 3 months for drug treatment window. For an individual who was exposed to two different medications since they entered GE network, we then examined if the second medication was within 3 months from the first one. If not, then the patient was then be classified as having monotherapy, and belonged to the drug group for whichever medication he/she got exposed to first. If the patient was exposed to 2 medications that's within 3 months, then he/she stayed in the more than 1 drug treatment group (combination therapy). Unlike claims data, in EMR, we could

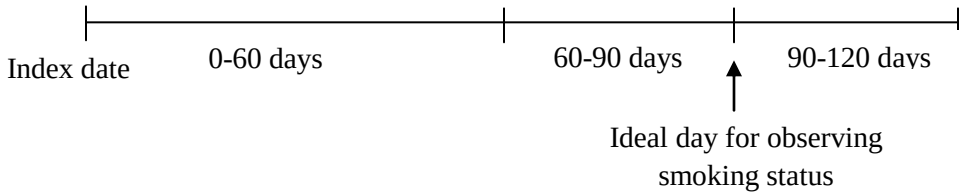
not be certain the second smoking cessation medication the patient got was a switch over or an add-on because many records for medication stop dates were missing. No record was found for an individual to have received both Bupropion and Varenicline within the 3-month exposure window since they entered the network. Therefore, we had a total of 5 smoking cessation groups: The individual had received (1) NRT only during the 3 months window, (2) Bupropion (Zyban) only during the 3 months window, (3) Varenicline only during the 3 months window, (4) NRT + Bupropion (Zyban) during the 3 months window, and (5) NRT + Varenicline during the 3 months window. The last 2 categories were classified together as combination therapy. The first day of being prescribed smoking cessation medication was defined as the index date.

For the short term outcome – 12 weeks (up to 16 weeks)

Though most of the medications are for 12 weeks, we observed our short term outcome up to the 16^{th} week. The reason for that is because sometimes patients may forget to take the medication on a daily basis. Instead of finishing up the medication in 12 weeks, it's common that they spent a little bit longer and finished by 16 weeks. Since it's highly likely the patients did not come back for an office visit on the exact 12^{h} week after index date, we took the observation on the day that's closest to the observation time. Three observation windows for smoking status were then constructed: (1) smoking status obtained between the next day of index date to day 60, (2) smoking status obtained between day 61 to day 90, and (3) smoking status obtained between day 91 to day 120. If a schizophrenic smoker had smoking status recorded in all three windows, then we took the observation preference as window #2, then window #3, and then window #1. We took the last smoking status observation in window #1 and #2, and took the first smoking

status observation in window #3 because those were closest times to day 90 (the ideal day for observing smoking status).

Figure 2. Smoking status for short term outcome



Smoking status was recorded in the file "text_observation_all". Smoking status was recorded as: assessed, current, ever, former, never, and not current. We kept the record for "current", "former", and "not current" only. Smoking status in other categories were not included because it is possible the smoking status that's closest to day 90 is "assessed" or "ever", which does not provide any information. Smoking status that being recorded as "current" closest to day 90 was counted as not reaching smoking abstinence, whereas being recorded as "not current" or "former" was counted as reaching abstinence.

<u>For the long term outcome – 1 year</u>

Quitting at week 12 (or up to week 16) is not enough to provide longer term abstinence, we want to see if the quitting effect will actually last. Furthermore, to follow the Russel Standard, we tracked the smoking status that is a year after the smoking medication exposure [57]. This long term model was to examine if the cessation product could help sustain the quitting effect. In this case, we considered if there was a second exposure to any of the smoking medication. The second exposure was from week 16 to year 1. Patients were categorized into eight medication

groups total: (1) Received only NRT during this period, (2) Received Bupropion (Zyban) only during this period, (3) Received Varenicline only during this period, (4) Received NRT and Bupropion (Zyban) during this period, (5) Received NRT and Varenicline during this period, (6) Received Bupropion (Zyban) and Varenicline during this period, (7) Received NRT, Bupropion (Zyban), and Varenicline during this period, and (8) did not have a second exposure to the medication during this period. Not too many patients were prescribed second exposure during this period; therefore, we categorized the variable as "had a second exposure vs. no second exposure during this timeline".

For smoking abstinence at year 1, we then had two models: (1) only included patients who quit at the 12th week, and (2) included all cohort whether they quit or not at week 12.

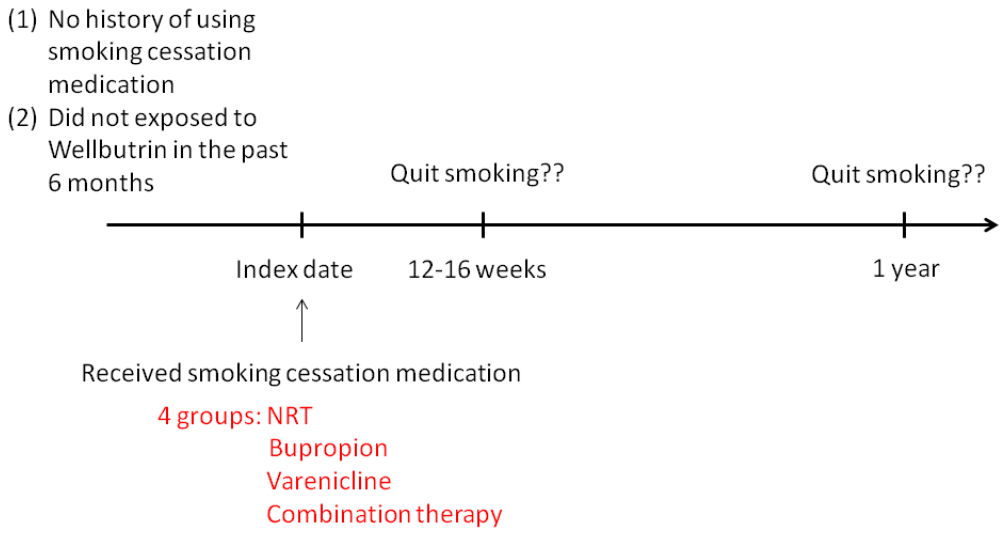
We took the smoking status that's closest to day 365 from the index date. Only the observations within one year were examined. We did not extend the observation for another month like we did for shorter term outcome because this was a second exposure to the cessation medications and we believed the medication is very likely to have an immediate effect on quitting.

Figure 3. Smoking status for long term outcome

As with the short term model, we kept the smoking status record for "current", "former", and "not current" only. Smoking status that being recorded as "current" closest to day 365 was

counted as not reaching smoking abstinence, whereas being recorded as "not current" or "former" was counted as reaching abstinence. Please see Figure 4 for the 1st objective analysis plan.

Figure 4: 1st Objective analysis plan



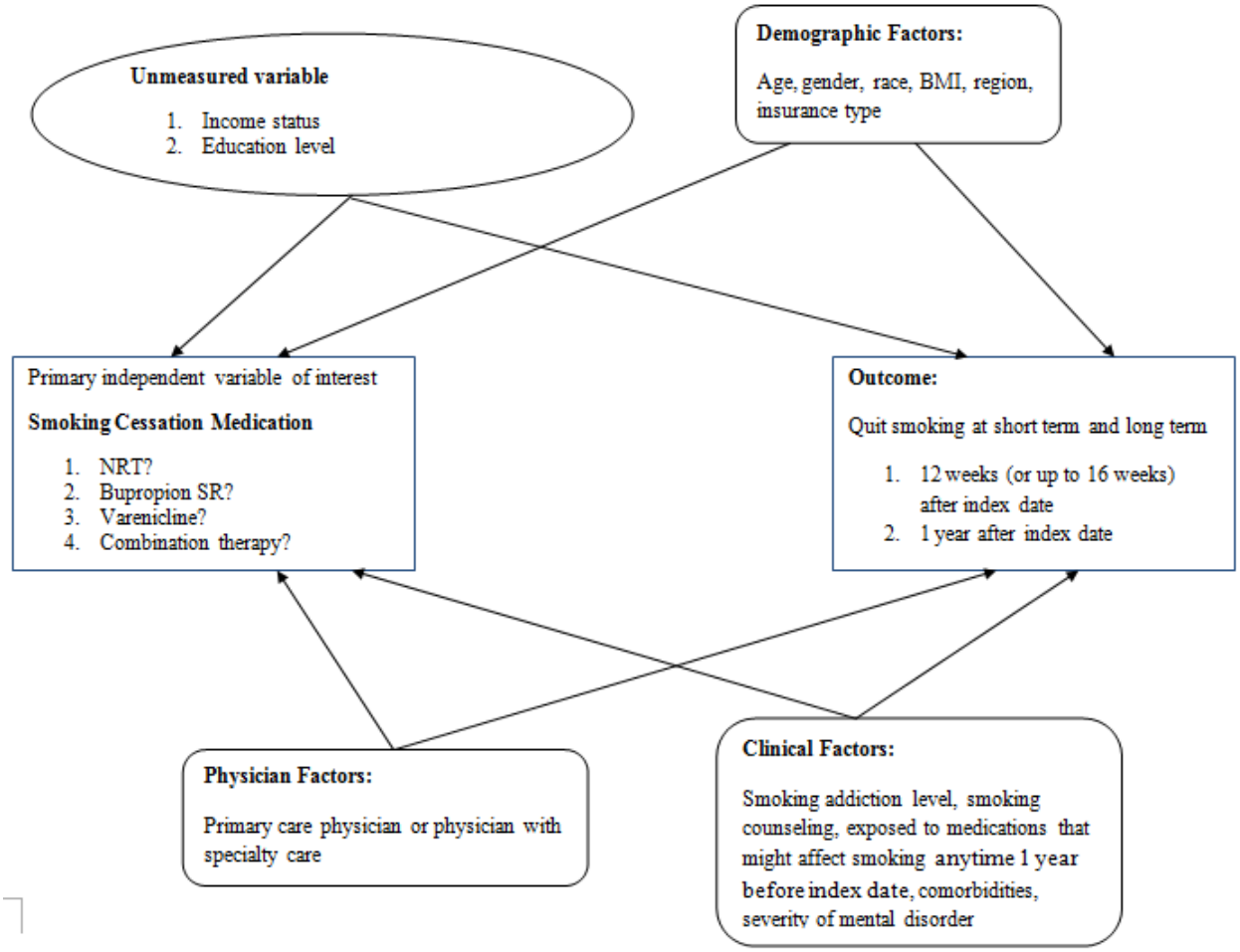
Logistic regression models were identified, and the dependent variables were the smoking status at three different outcomes as previously mentioned: (model 1a) Quitting at 12th week (or up to 16th week) after index date, (model 1b) Quitting at 1 year among those who quit at week 12, and (model 2) Quitting at 1 year after index date (regardless of the smoking status at week 12).

Independent variable of primary interest was the cessation product (NRT, Bupropion SR, Veranicline or combination therapy), other independent variables that were included in the models included: age, race, gender, BMI (normal, overweight, or obesity), region (Midwest, Northeast, South, West), payment type (government or not government insurance), specialty group (primary care or specialty care doctor that prescribed the medication), smoking addiction level, smoking counseling, exposure to medications that might affect their smoking status (nortriptyline, buspirone, clonidine, naltrexone, mecamylamine, or rimonabant) anytime 1 year

before index date, comorbidity index (D'Hoore), and severity of mental disorder (having antipsychotic injections anytime one year before index date was considered as severe). The independent variables for 1 year model were the same as the short term model, but we added an extra variable for model 1b and model 2: having an exposure to any of the cessation product between week 16 to year 1 (yes/no), and another variable for model 2: quit smoking at week 12 (yes/no).

Level of nicotine dependence (Fagerstrom Test) including how many cigarettes they smoke per day [6] was not recorded but we could infer that from the NRT dose they were taking. If their starting dose for nicotine patch was 21mg/day or nicotine gum 4mg/piece then they were classified as high nicotine addiction; on the other hand, if their starting dose for nicotine patch was 14mg/day or 7mg/day, or nicotine gum 2mg/piece, then they were classified as low nicotine addiction. However, for those who were on Bupropion or Varenicline, they all were classified as high nicotine addiction because those doses were fixed for all smokers. They were assumed to have higher addiction level because they did not take the more easily accessible NRT. Some variables that may influence abstinence but are not available in the dataset included: income status [77] and education level. However, studies have shown that most of the schizophrenic patients are unemployed, with a low income, and low educational attainment [78]. Thus, even though GE data doesn't provide information about the income status or education level, it could be assumed they are somewhat similar. Figure 5 below shows the conceptual model for quitting smoking.

Figure 5. Conceptual model for quitting smoking



In order to examine if there were any characteristic differences between patients using different medications, we first carried out chi-square analyses. After that, the second step descriptive statistics and chi-square analyses were again used to determine the frequencies and associations of patient characteristics with the two timelines abstinence outcomes. Multiple logistic regression models were then be carried out to determine the predictors of successful cessation. The primary variable of interest was cessation product that would lead to higher chances of quitting at two different points in time. All the variables with a p-value <0.2 in chi-sq as well as the possible counfounding variables were included in the logistic models. Prior to conducting the multiple logistic regressions, co-linearity between the independent variables was

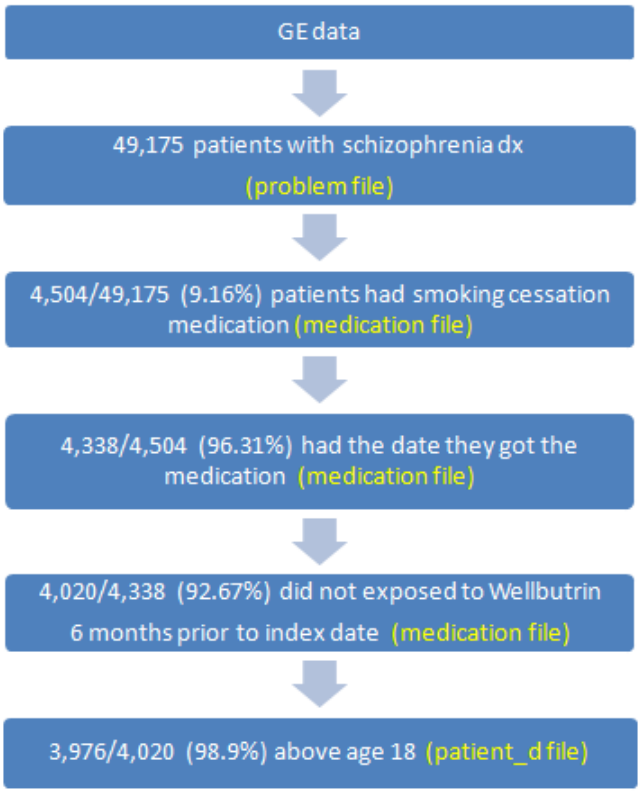
first assessed, and if we were to find two independent variables that are highly correlated with each other, one variable that we think is less influential towards the outcomes would be dropped. Characteristics like age, gender, and race were included regardless of the significant results in chi-sq analysis. Interaction terms between variables were tested as well. All statistical analyses were carried out using SAS statistical package version 9.3.

RESULTS

Baseline Sample Characteristics

From the inception of GE data, we found there are a total of 49,175 patients had at least one diagnosis of schizophrenia or schizoaffective disorder (from December 1995 to October 2011). About 10% of them were prescribed at least one cessation medication at any point (n=4,504, 9.16%). Most of the dates they received the medication prescription were recorded (n=4338, 96.31%) and for those without the dates were dropped. To meet our study exclusion criteria "individual aged below 18 years old" or "those who received antidepressants Bupropion (Wellbutrin®) at any point 6 months prior to index date" were also dropped from our study cohort. This brought us down to a total of 3,976 patients. Please see Figure 6 below for our study cohort.

Figure 6. Our study cohort



For 1st objective – cohort distribution

Slightly more than half were with male gender (n=2,141, 53.85%), close to half were whites (n=1,805, 45.40%), and majority were with high nicotine addiction level (n=3,202, 80.53%). Most of them had stable mental state as only 2.39% (n=95) of the cohort had antipsychotics in the injection form at any point 1 year prior to index date. Slightly more than half (n=2,045, 53.62%) of the cessation medication users were under Medicare or Medicaid coverage. The mean age of the cohort was 45.40 years old (± SD: 11.51) with a minimum of 18 and a maximum of age 80. Most of the cessation medications were given by their primary care physicians (n=3,858, 97.03%) and about forty percent of the patients had received smoking counseling from their healthcare providers during the one year prior to index date (n=1,606, 40.39%). The medications were being prescribed to patients across the nation with the highest percentage in the Northeast part (n=1,278, 32.17%) and the lowest in the West part (n=679,

17.09%). Please see Table 1 and table 2 for patients' characteristics by the cessation medication types and outcomes.

Table 1. Overall baseline characteristics of our cohort and numbers (percentages) within each cessation medication

Characteristics	Overall cohort Total Frequency (Percentage)	Varenicline N=1164 (29.28)	NRT N=2590 (65.14)	Bupropion N=89 (2.24)	Combo N=133 (3.35)	p-values
Demographics						
Sex						
Female	1,835 (46.15)	537 (46.13)	1,179 (45.52)	51 (57.30)	68 (51.13)	0.1026
Male	2,141 (53.85)	627 (53.87)	1,411 (54.48)	38 (42.70)	65 (48.87)	
Age (years)						0.5548
Race						
Blacks	622 (15.64)	119 (10.22)	474 (18.30)	14 (15.73)	15 (11.28)	**<0.0001***
Whites	1,805 (45.40)	566 (48.63)	1,147(44.29)	34(38.20)	58 (43.61)	
All others	1,549 (38.96)	479 (41.15)	969 (37.41)	41 (46.07)	60 (45.11)	
Region						
Midwest	1,089 (27.41)	261 (22.44)	781 (30.18)	11 (12.36)	36 (27.07)	
Northeast	1,278 (32.17)	282 (24.25)	927 (35.82)	25 (28.09)	44 (33.08)	**<0.0001***
South	927 (23.33)	345 (29.66)	510 (19.71)	38 (42.70)	34 (25.56)	
West	679 (17.09)	275 (23.65)	370 (14.30)	15 (16.85)	19 (14.29)	
BMI						
Normal (BMI<25)	1,483 (37.30)	427 (36.68)	963 (37.18)	39 (43.82)	54 (40.60)	0.5534
Overweight (25<=BMI<30)	874 (21.98)	251 (21.56)	583 (22.51)	18 (20.22)	22 (16.54)	
Obesity (BMI>=30)	1,619 (40.72)	486 (41.75)	1,044 (40.31)	32 (35.96)	57 (42.86)	
Insurance						
Not Medicare/Medicaid	1,769 (46.38)	496 (44.52)	1,181 (47.49)	47 (55.95)	45 (34.88)	**0.0053***
Medicare or Medicaid	2,045 (53.62)	618 (55.48)	1,306 (52.51)	37 (44.05)	84 (65.12)	
Clinical factors						
Comorbidty Index						**0.0027***
Had antipsychotic injectables 1 year prior to index date						
No	3,881 (97.61)	1141 (98.02)	2,526 (97.53)	88 (98.99)	126 (94.74)	0.1001
Yes	95 (2.39)	23 (1.98)	64 (2.47)	1 (1.12)	7 (5.26)	
Smoking Cessation Related						
Addicted to nicotine						**<0.0001***

No	774 (19.47)	0 (0.0)	752 (29.03)	0 (0.0)	22 (16.54)	
Yes	3,202 (80.53)	1,164 (100.0)	1,838 (70.97)	89 (100.0)	111 (83.46)	
Cessation Rx given by specialty care physician?						
No	3,858 (97.03)	1120 (96.22)	2,521 (97.34)	88 (98.99)	129 (96.99)	0.2080
Yes	118 (2.97)	44 (3.78)	69 (2.66)	1 (1.12)	4 (3.01)	
Received any medication that might affect smoking status anytime 1 year prior to index date						
No	3,796 (95.47)	1127 (96.82)	2,463 (95.10)	83 (93.26)	123 (92.48)	**0.0232***
Yes	180 (4.53)	37 (3.18)	127 (4.90)	6 (6.74)	10 (7.52)	
Smoking counseling received anytime one year prior to index date						
No	2,370 (59.61)	721 (61.94)	1,503 (58.03)	61 (68.54)	85 (63.91)	**0.0258***
Yes	1,606 (40.39)	443 (38.06)	1,087 (41.97)	28 (31.46)	48 (36.09)	
Total cohort=3,976; * p≤0.05						

Table 2. Abstinence at week 12 (or 16) and year 1 among schizophrenic smokers who were prescribed any smoking cessation medication

Characteristics	Model 1a Abstinence at week 12 or 16 (n=235, 18.02%)		Model 1b Abstinence at year 1 among those quit at week 12 or 16 (n=170, 75.22%)		Model 2 Abstinence at year 1, regardless of quitting at week 12 or 16 (n=346, 17.20%)	
	Number (%)	p-value	Number (%)	p-value	Number (%)	p-value
Demographics						
Sex						
Female	111 (17.99%)	0.9778	77 (71.30%)	**0.1910***	170 (17.86%)	0.4570
Male	124 (18.05%)		93 (78.81%)		176 (16.60%)	
Race						
Blacks	19 (10.27%)	**0.0025***	12 (63.16%)	0.4207	29 (9.93%)	**0.0010***
Whites	112 (17.53%)		85 (77.27%)		188 (19.26%)	
All others	104 (21.67%)		73 (72.26%)		129 (17.34%)	
Region						
Midwest	76 (19.34%)		54 (75.00%)		88 (15.20%)	
Northeast	69 (14.20%)	**<0.0001***	45 (67.16%)	**0.1996***	120 (16.19%)	**0.0024***
South	34 (14.05%)		29 (85.29%)		65 (16.33%)	
West	56 (30.60%)		42 (79.25%)		73 (24.83%)	
BMI						
Normal (BMI<25)	83 (19.53%)	0.3187	65 (80.25%)	**0.1132***	123 (18.25%)	0.6707
Overweight (25<=BMI<30)	44 (15.17%)		35 (81.40%)		77 (16.81%)	
Obesity (BMI>=30)	108 (18.34%)		70 (68.63%)		146 (16.59%)	
Insurance						
Not Medicare/Medicaid	95 (16.46%)	0.2834	63 (72.41%)	0.2153	131 (14.57%)	**0.0057***
Medicare or Medicaid	129 (18.78%)		102 (79.69%)		200 (19.32%)	
Clinical factors						
Had antipsychotic injectables 1 year prior to index date						
No	228 (18.01%)	0.9481	164 (74.89%)	0.5136	334 (17.03%)	0.2248
Yes	7 (18.42%)		6 (85.71%)		12 (23.53%)	

Smoking Cessation Related						
Addicted to nicotine						
No	39 (15.54%)	0.2546	31 (81.58%)	0.3196	62 (16.36%)	0.6313
Yes	196 (18.61%)		139 (73.94%)		284 (17.39%)	
Cessation Medication						
Varenicline	73 (21.04%)		57 (78.08%)		112 (20.07%)	
NRT	153 (17.43%)	**0.1300***	113 (73.86%)	0.4914	215 (16.09%)	**0.2038***
Bupropion SR	4 (18.18%)		n/a		5 (14.29%)	
Combination	5 (8.77%)		n/a		14 (16.87%)	
Cessation Rx given by specialty care physician?						
No	224 (17.67%)	**0.0472***	163 (75.46%)	0.6957	337 (17.12%)	**0.5119***
Yes	11 (30.56%)		7 (70.00%)		9 (20.93%)	
Received any medication that might affect smoking status anytime 1 year prior to index date						
No	226 (18.20%)	0.4619	n/a	n/a	330 (18.20%)	0.8878
Yes	9 (14.52%)				16 (14.52%)	
Smoking counseling received anytime one year prior to index date						
No	133 (22.13%)	**0.0004***	97 (76.38%)	0.6482	200 (19.90%)	**0.0013***
Yes	102 (14.51%)		73 (73.74%)		146 (14.50%)	
Had the 2nd cessation exposure during week 16 – 1 year						
No	n/a	n/a	134 (81.71%)	**0.0002***	245 (16.42%)	**0.1182***
Yes			36 (58.06%)		101 (19.42%)	
Abstinence at week 12						
No	n/a	n/a	n/a	n/a	62 (5.80%)	**<0.0001***
Yes					175 (74.47%)	
• Total frequency for model 1a=3,976; Total frequency for model 1b=226; Total frequency for model 2=3,976; **P<0.2**						

As shown in Table 1, NRT was the most commonly used cessation medicationas compared to Bupropion SR and Varenicline. With the 3-month treatment window, about two thirds of the cohort were prescribed NRT only (n=2,590, 65.14%), followed by Varenicline (n=1,164, 29.28%), and the lowest rate was with Bupropion (n=89, 2.24%). A portion of patients were prescribed two medications within 3 months window: NRT + Varenicline (n=112, 2.82%) and NRT + Bupropion (n=21, 0.53%). No records were found for any individual to receive Bupropion and Varenicline during the same period. Due to small sample size of those who got more than 2 medications, we grouped them together into "combination group" in further logistic regression models.

<u>For 1st objective – short term abstinence at week 12 (or week 16) – model 1a</u>

Among the 3,976 cohort who were prescribed cessation medication, approximately one third had smoking status recorded at week 12 (n=1,304, 32.80%). The other two thirds (67.20%) did not have the status recorded and were dropped from the short term analysis. Average short term smoking status was assessed at 66.72 days after the medication exposure.

The overall abstinence was 18.0% with Varenicline being the highest (21.0%), followed by Bupropion SR (18.2%), NRT (17.4%), NRT + Bupropion SR (14.3%) and lastly NRT + Varenicline (8.0%). Please refer to Table 3 below for detailed abstinence information within each treatment group. Besides the medication, our main variable of interest, whether other independent variables have an effect on the outcome could be found in the results of the chi-square analyses in Table 2.

Table 3. Abstinence within each treatment group for the short term.

	# of patients who were exposed to the drug	Had smoking status recorded within month 3	Quit smoking at the last observation	Percentage of successful quitting
1. NRT	2,590	878	153	17.4%
2. Varenicline	1,164	347	73	21.0%
3. Bupropion	89	22	4	18.2%
Combination				
4. NRT + Varenicline	112	50	4	8.0%
5. NRT + Buprpion	21	7	1	14.3%
Total	3,976	1,304	235	18.0%

For 1st objective – long term abstinence at year 1 among those who quit at week 12 - model 1b

Among the 235 schizophrenic patients who quit smoking at week 12, we continued follow up time until one year to see if their quitting behavior sustained. Some of the individuals (n=64, 27.23%) went back to the smoking behavior and got exposed to the cessation medication again during this period (between week 16 to year 1). This means almost one third of the quitting effect did not sustain. It is very likely the 2nd exposure they got during this period is the same as what they were prescribed with the index medication. As shown in the following tables, Bupropion seems to help smokers keep the quitting behavior for the long term as all 4 patients who quit at week 12 also reported not smoking at year 1. Group NRT as index medication and group Varenicline as index medication had very similar quitting rate at year 1 (73.86% for NRT and 78.08% for Varenicline). Sustained long term abstinence was the lowest among those who belonged to the combination group with only 1 of them quit smoking among five patients (20%). Please refer to Table 4 below for detailed continuous abstinence information within each treatment group. Besides the medication, our main variable of interest, whether other independent variables had an effect on the outcome could be found in the results of the chi-square analyses in Table 2.

Table 4. Long term abstinence among those who quit at week 12

1st exposure and quit at week 12	2nd exposure (between week 16 – year 1)		Quit smoking at year 1	Percentage of successful quitting
NRT: 153	NRT	34 (22.22%)	21	61.8%
	Varenicline	3 (1.96%)	1	33.3%
	Bupropion	0	n/a	n/a
	No treatment	116 (75.82%)	91	78.5%
		OVERALL	113	113/153=73.86%

1st exposure and quit at week 12	2nd exposure (between week 16 – year 1)		Quit smoking at year 1	Percentage of successful quitting
Varenicline: 73	NRT	3 (4.11%)	0	0
	Varenicline	22 (30.14%)	14	63.6%
	Bupropion	0	n/a	n/a
	No treatment	48 (65.75%)	43	89.6%
		OVERALL	57	57/73=78.08%

1st exposure and quit at week 12	2nd exposure (between week 16 – year 1)		Quit smoking at year 1	Percentage of successful quitting
Bupropion: 4	NRT	0	n/a	n/a
	Varenicline	0	n/a	n/a
	Bupropion	0	n/a	n/a
	No treatment	4 (100%)	4	100%
		OVERALL	4	4/4=100%

1st exposure and quit at week 12	2nd exposure (between week 16 – year 1)		Quit smoking at year 1	Percentage of successful quitting
Combination: 4 + 1	NRT	1 (20%)	0	0
	Varenicline	0	n/a	n/a
	Bupropion	1 (20%)	0	0
	No treatment	3 (60%)	1	33.3%
		OVERALL	1	1/5=20%

For 1st objective – long term abstinence at year 1 among all cohort - model 2

Among the 3,976 cohort who received cessation medication, approximately half had smoking status recorded at year 1 (n=2,012, 50.60%). The rest did not have the status recorded so they were dropped from the analysis. Average long term smoking status was assessed at 209.52 days after the medication exposure.

Among the 2,012, the overall abstinence was 17.20% with 346 schizophrenic smokers quit at year 1: Varenicline being the highest cessation rate (20.1%), followed by combination treatment (16.9%), NRT (16.1%), and lastly Bupropion (14.3%). Please refer to Table 5 below for detailed abstinence information within each treatment group. Besides the medication, our main variable of interest, whether other independent variables have an effect on the outcome could be found in the results of the chi-square analyses in Table 2.

Table 5. Abstinence within each treatment group for the long term.

	# of patients who were exposed to the drug	Had smoking status recorded closest to year 1	Quit smoking at the last observation	Percentage of successful quitting
1. NRT	2,590	1,336	215	16.1%
2. Varenicline	1,164	558	112	20.1%
3. Bupropion	89	35	5	14.3%
Combination				
4. Combination (N+V or N+B)	112	83	14	16.9%
Total	3,976	2,012	346	17.2%

Table 6 below gives an overall summary of quitting smoking at the two time frames with our schizophrenia cohort. It indicates that whether they succeed in quitting in the long term could be inferred from if they quit in the short term. Among the 237 patients who quit at 1 year, 175 (73.84%) also reported not smoking at the 12th week; on the other hand, among the 1,067

patients who did not succeed in quitting at 1 year, 1,007 (94.38%) of them were also still smoking at the 12th week.

Table 6. Smoking status at two point in time within our cohort

	Quit smoking at year 1	Did not quit at year 1	
Quit smoking at week 12	175	60	235
Did not quit at week 12	62	1,007	1,069
	237	1,067	

Logistic regression model for short term abstinence – model 1a

Univariate and multivariate logistic regression results are presented in Table 7. We examined the interaction effect: our primary interest variable (cessation medications) interacts with other independent variables using chunck test. The model with all the interaction terms was not statistically different from the model without the interactions: likelihood ratio difference between the two models (all independent variables and all independent variables + interactions) was 54.472, giving a non significant p-value between 0.05 – 0.1 at 45 degrees of freedom.

In the multivariate models (adjusted rates), we found that older adults were more likely to quit smoking: as one year increase in age, the chance of quitting increased by 2% (OR=1.02, 95% CI=1.01 – 1.03). As compared to Blacks, Whites (OR=1.83, 95% CI=1.04 – 3.20) and all other races (Asians, Hispanics, Multi-races, and Indian Americans) (OR=2.13, 95% CI=1.19 – 3.79) were more likely to quit smoking. Those whose household locations were in the west part of U.S. were also more likely to achieve quitting at short term as compared to those in the Midwest (OR=2.18, 95% CI=1.39 – 3.41). No significant differences were found between cessation medications; however, those who had combination treatment within 3 months treatment window

were slightly less likely to quit compared to Varenicline but this did not reach statistical significance. The p-value was very close to reaching a significant level (OR=0.38, 95% CI=0.15 – 1.00). Individuals who had received smoking counseling anytime one year prior to index date were actually less likely to quit compared to those who did not have counseling from their healthcare providers (OR=0.67, 95% CI=0.49 – 0.92).

Logistic regression model for long term abstinence at year 1 among those who quit at week 12 - model 1b

In this analysis, we were only looking at schizophrenic patients who were prescribed Varenicline and NRT since the sample size was low for those who were prescribed Bupropion (n=4) or combination (n=1) that reached sustained abstinence at year 1. No interactions were found between the cessation medications and other independent variables using chunck test. The model with all the interaction terms was not statistically different from the model without the interactions: likelihood ratio difference between the two models (all independent variables and all independent variables + interactions) was 4.511, giving a non significant p-value > 0.1 at 15 degrees of freedom.

Most of the characteristics or factors we included in the model were all not significantly associated with quitting at one year except one variable – whether they received a second cessation medication from week 16 to year 1. Patients who had a 2nd exposure were less likely to quit smoking compared to those without the 2nd time exposure (OR=0.26, 95% CI=0.13 – 0.55).

Logistic regression model for long term abstinence at year 1 among all cohort - model 2

In this model, we were able to make comparisons between all cessation medication groups because we had more patients who quit smoking at year 1 (comparing to model 1b) as

this is for all cohorts and not specifically among those who quit at week 12. No interactions were found between the cessation medications and other independent variables using chunck test. The model with all the interaction terms was not statistically different from the model without the interactions: likelihood ratio difference between the two models (all independent variables and all independent variables + interactions) was 60.826, giving a non significant p-value between 0.1 – 0.2 at 51 degrees of freedom.

Similarly, we were not able to find many significant differences for medications in reaching higher cessation level. As shown in Table 5, the best character to predict cessation at year 1 was whether they quit or not at week 12. Those who quit at week 12 were also more likely to quit at one year (OR=56.49, 95% CI=36.48 – 87.49).

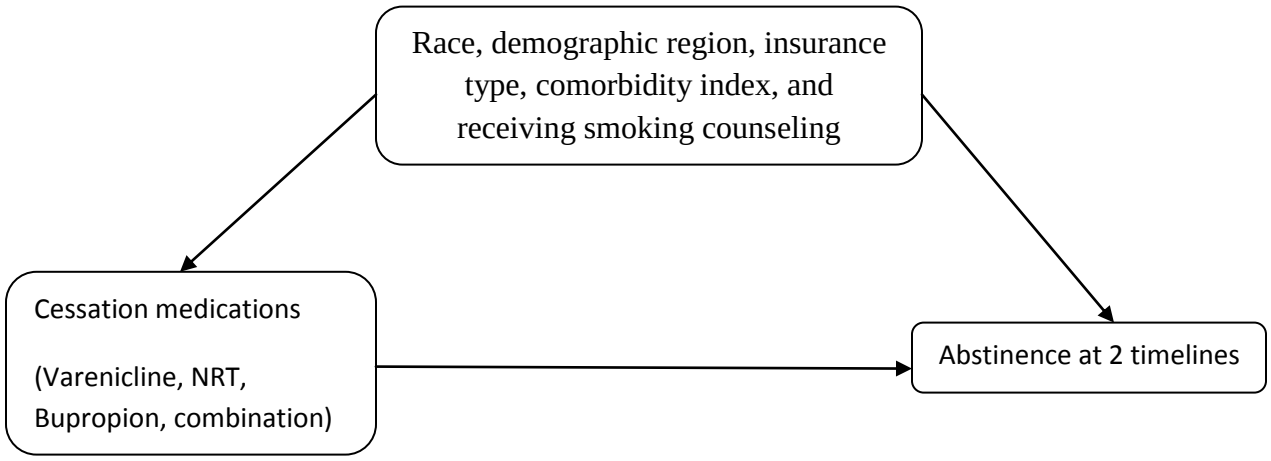
Other significant characteristics that we found significantly affect smoking abstinence at week 12 or 1 year included older age, Medicare/Medicaid enrollees, without smoking counseling, and those whose residential region located in the West part of the nation.

Table 7. Logistic regression models for quitting at week 12 (or 16) and year 1 among schizophrenic smokers

	Model 1a - Abstinence at week 12 or 16		Model 1b - Abstinence at year 1 among those who quit at week 12 or 16		Model 2 - Abstinence at year 1 (regardless of quitting at week 12 or 16)	
Characteristics	Unadjusted ORs	Adjusted ORs (c=0.653)	Unadjusted ORs	Adjusted ORs (c=0.883)	Unadjusted ORs	Adjusted ORs (c=0.881)
Demographics						
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.01 (0.76 –1.34)	1.07 (0.79 –1.44)	1.50 (0.82 –2.75)	1.49 (0.74 –3.03)	0.92 (0.73 –1.16)	0.82 (0.54 –1.24)
Age (years)	1.01 (0.99 –1.03)	**1.02 (1.01 –1.03)***	1.01 (0.99 –1.04)	1.01 (0.98 –1.04)	1.01 (0.99 –1.02)	1.02 (0.99 –1.04)
Race						
Blacks	Reference	Reference	Reference	Reference	Reference	Reference
Whites	**1.86 (1.11 –3.12)***	**1.83 (1.04 –3.20)***	1.99 (0.71 –5.58)	2.05 (0.60 –7.02)	**2.17 (1.43 –3.28)***	1.58 (0.78 –3.20)
All others	**2.42 (1.44 –4.08)***	**2.13 (1.19 –3.79)***	1.78 (0.63 –5.02)	1.77 (0.50 –6.28)	**1.91 (1.24 –2.92)***	1.41 (0.67 –2.97)
Region						
Midwest	Reference	Reference	Reference	Reference	Reference	Reference
Northeast	**0.69 (0.49 –0.99)***	0.88 (0.59 –1.31)	0.69 (0.33 –1.43)	0.60 (0.24 –1.51)	1.08 (0.80 –1.46)	1.32 (0.76 –2.31)
South	0.69 (0.44 –1.06)	0.94 (0.58 –1.53)	1.94 (0.66 –5.75)	1.50 (0.44 –5.18)	1.09 (0.77 –1.55)	1.52 (0.79 –2.92)
West	**1.84 (1.24 –2.75)***	**2.18 (1.39 –3.41)***	1.28 (0.55 –2.99)	1.43 (0.49 –4.24)	**1.85 (1.31 –2.62)***	1.86 (0.96 –3.62)
BMI						
Normal (BMI<25)	Reference	Reference	Reference	Reference	Reference	Reference
Overweight (25<=BMI<30)	0.74 (0.50 –1.10)	0.78 (0.51 –1.19)	1.08 (0.42 –2.77)	0.92 (0.32 –2.66)	0.91 (0.67 –1.24)	1.07 (0.62 –1.84)
Obesity (BMI>=30)	0.93 (0.68 –1.28)	1.04 (0.74 –1.47)	0.54 (0.27 –1.08)	0.62 (0.28 –1.38)	0.90 (0.69 –1.16)	0.66 (0.41 –1.07)
Insurance						
Not Medicare/Medicaid	Reference	Reference	Reference	Reference	Reference	Reference
Medicare or Medicaid	1.18 (0.88 –1.57)	1.16 (0.85 –1.58)	1.50 (0.79 –2.83)	1.53 (0.75 –3.15)	**1.41 (1.11 –1.79)***	1.28 (0.84 –1.95)
Clinical factors						
Comorbidty Index	0.97 (0.89 –1.05)	0.92 (0.84 –1.01)	0.95 (0.80 –1.12)	1.15 (0.92 –1.45)	0.94 (0.88 –1.01)	0.94 (0.83 –1.07)
Had antipsychotic injectables 1 year prior to index date						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.03 (0.45 –2.37)	1.02 (0.44 –2.40)	2.02 (0.24 –17.09)	1.22 (0.12 –12.40)	1.50 (0.78 –2.90)	1.71 (0.57 –5.13)

Smoking Cessation Related						
Addicted to nicotine						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.25 (0.86 –1.81)	1.07 (0.71 –1.62)	0.65 (0.27 –1.55)	0.59 (0.21 –1.64)	1.08 (0.80 –1.46)	0.89 (0.51 –1.55)
Cessation Medication						
Varenicline	Reference	Reference	Reference	Reference	Reference	Reference
NRT	0.80 (0.58 –1.09)	0.89 (0.63 –1.27)	0.80 (0.41 –1.54)	0.63 (0.29 –1.42)	**0.77 (0.60 –0.99)***	0.95 (0.59 –1.54)
Bupropion SR	0.84 (0.28 –2.54)	1.04 (0.33 –3.34)	n/a	n/a	0.67 (0.26 –1.75)	1.58 (0.38 –6.59)
Combination	**0.37 (0.14 –0.94)***	0.38 (0.15 –1.00)	n/a	n/a	0.81 (0.44 –1.49)	0.78 (0.25 –2.40)
Cessation Rx given by specialty care physician?						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	2.06 (0.99 –4.23)	2.09 (0.97 –4.48)	0.76 (0.19 –3.04)	0.45 (0.09 –2.20)	1.29 (0.61 –2.70)	0.50 (0.15 –1.63)
Received any medication that might affect smoking status anytime 1 year prior to index date						
No	Reference	Reference	n/a	n/a	Reference	Reference
Yes	0.77 (0.38 –1.57)	0.96 (0.46 –2.04)			0.97 (0.56 –1.67)	2.18 (0.93 –5.09)
Smoking counseling received anytime one year prior to index date						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	**0.60 (0.45 –0.80)***	**0.67 (0.49 –0.92)***	0.87 (0.48 –1.60)	0.90 (0.44 –1.84)	**0.69 (0.54 –0.87)***	0.72 (0.47 –1.10)
Had the 2nd cessation exposure during week 16 – 1 year						
No	n/a	n/a	Reference	Reference	Reference	Reference
Yes			**0.31 (0.17 –0.59)***	**0.26 (0.13 –0.55)***	1.23 (0.95 –1.59)	0.77 (0.48 –1.25)
Abstinence at week 12						
No					Reference	Reference
Yes	n/a	n/a	n/a	n/a	**47.38 (32.09 –69.94)***	**56.49 (36.48 –87.49)***
OR: Odds Ratio; 95% CI: 95% Confidence Interval; ***$p \leq 0.05$.**						

We examined the relationships between "cessation medications + cohort characteristics", "cohort characteristics + abstinence outcomes" and "cessation medications + abstinence outcomes"; we could therefore infer the confounders in our multiple logistic regression models. We found race, demographic region, insurance type, comorbidity index, and receiving smoking counseling were confounders that affect both the cessation medication exposure and our abstinence outcomes.



DISCUSSION

Our study objectives were to compare abstinence rates with different smoking cessation medications (NRT, Bupropion, Varenicline) among schizophrenic patients. Abstinence rate was about 18.02% at week 12 and 17.20% at year 1. Among those who quit at 12^{th} week, about 75.22% of the quitting effect sustained at 1 year.

The majority of the 3,976 cohort who were prescribed cessation medications (n=3,881, 97.61%) had stable mental states as they did not have any antipsychotics in injection forms one year prior to index date. This indicates that healthcare system may have been reluctant to prescribe cessation products to those without stable mental states. A potential reason could be

the possible beneficial effect of tobacco, which could be used to alleviate some of the symptoms in schizophrenia and reduce the side-effects of antipsychotic medications [23]. Another reason might be that in comparison to the unpredictable positive and negative schizophrenic symptoms, smoking seems to be a small problem and not the primary focus of healthcare providers.

Among the cohort were prescribed cessation medications, almost half were whites (n=1,805, 45.40%), followed by other races (Asians, Hispanics, Multi-races, and Indian Americans) (n=1,549, 38.96%), and blacks (n=622, 15.64%). Compared to all other races, the quit rates were the lowest for blacks among all three models and, similarly, quitting odds were significantly lower in the first logistic regression model (model 1a) after adjusting for other possible confounding factors. Previous studies have reported racial inequalities in prescribing as well as racial differences in successful quitting among those who were prescribed cessation medications. The causes of these disparities are multi-factorial and complex [79]. Barriers to receipt of treatment could be due to lack of health-insurance coverage or geographic location. Another possible reason could be that blacks were less likely to receive healthcare providers' advices to quit than whites [79, 80]. However, some previous trials targeted to minority smokers like blacks have demonstrated the efficacy of a variety of smoking cessation treatments provided to them [79]. Therefore, physicians should provide all available cessation strategies to smokers regardless of their races and future research should examine and address reasons for the observed racial disparities.

Medicaid enrollees are reported to have nearly twice the smoking rates of the general adult population [81]. Schizophrenic smokers are usually with lower social-economic statuses thus more likely to be covered under Medicaid. In our study, we found slightly more than half of the cessation medications were prescribed to smokers who are under Medicare or Medicaid

coverage (n=2,045, 53.62%). Abstinence rates were also higher for those who were insured under the governmental health insurance compared to those with private insurance in both short term (18.78% vs. 16.46%) and long term (79.69% vs. 72.41% for continuous abstinence and 19.32% vs. 14.57% at year 1). This could be related to the coverage of tobacco cessation in the Medicaid program, which was a part of all states' plans by 2002 [82]. A study surveyed Medicaid programs in the 50 states and the District of Columbia (DC) to document their 2009 tobacco-dependence treatment plan and found that 47 programs offered coverage [81]. However, when we conducted multiple logistic regression, insurance type was no longer a significant predictor in all three models.

Of the 3,976 patients who were prescribed cessation medications, only 40% of them received smoking cessation counseling during the one year prior to index date (n=1,606, 40.39%). Health professionals are at the forefront of tobacco epidemics as they consult millions of people and can encourage them to quit smoking. In developed countries, more than 80% of the population see a primary care physician at least once a year, and doctors are perceived to be influential sources of information for smoking cessation [83]. Patients see physicians as valuable and credible sources of health information, and patients generally adhere to physician advice [84]. Our results, similarly, showed that the cessation medications were mostly prescribed by their primary care doctors as well (n=3,858, 97.03%). Primary care physicians should take this chance to broaden the reach of effective smoking-cessation counseling. It is difficult to ask schizophrenic patients to suddenly quit smoking. Providing them with anti-smoking messages from time to time would be helpful in getting these patients ready for quitting and support a successful cessation. With the low level of counseling documented in this study, there is a need to evaluate the potential reasons and improve these rates for future research.

Among all the medications, NRT was the most commonly prescribed (n=2590, 65.14%). This could be because NRT products are mostly OTCs and easily accessible at pharmacies or grocery stores. The approval of Bupropion SR (Zyban®) was after NRT, but it was not that commonly prescribed by physicians in this patient population. Prescription rate for Bupropion (Zyban®) (n=89, 2.24%) was even lower than the most recent approved Varenicline (n=1164, 29.28%). In our cohort of schizophrenic patients, hallucinations and depression symptoms are common comorbid conditions. One would expect physicians to prescribe Bupropion more frequently as it could be used for treating depression and reducing smoking cravings at the same time. Among smokers with a history of depression, there is a twofold higher risk of experiencing recurrent depressive episodes in the one year following cessation from smoking [85]. Even among those who did not originally have negative emotions, a large proportion demonstrated a depressed mood after quitting [85]. The low prescription percentage we observed here could be due to insurance coverage issues. Insurance companies are more likely to cover depression medications compared to cessation medications, therefore, Zyban® is less likely to be covered under their policies but the same ingredients product Wellbutrin® is usually covered. For instance, the Community Health Plan of Washington (CHPW) did not cover bupropion SR for smoking cessation in 1999, but the plan did cover bupropion (Wellbutrin®) for mental health indications [86]. When physicians want to prescribe Bupropion to their patients, they might rather prescribe Wellbutrin® but not Zyban® for lower out of pockets expenses for patients. Thus the low rate of Buproprion use (n=89, 2.24%) could be under estimated.

We found the overall quitting rate for the short term was 18.02% with Varenicline being highest (21.04%), followed by Bupropion (18.18%), NRT (17.43%) and combination treatment being the lowest (8.77%). The quitting rate was not low and suggested that it is possible for

schizophrenic patients to stop smoking. Healthcare professionals should consider that quitting smoking is not impossible for individuals suffering from schizophrenia. Since there was no head to head comparison study between medications, we could not examine if our findings are consistent with previous research, but we could compare abstinence within each medication that was conducted specifically among schizophrenic smokers. Our NRT quitting rate fell between two previous studies: about 27% in a 2004 RCT by Chou et al. (7/26 smokers quit smoking at 12^{th} week follow-up) [49] and 5% for a 2012 RCT by Chen et al. (4/92 smokers quit at 8^{th} week after exposure) [50]. Our Varenicline group quitting rate was close to the one found in a RCT by Williams et al. (19.05%) [55] and was significantly lower than the finding by Weiner et al. (75%, 3/4 smokers not smoking at week 9, 10, 11, and 12) [54]. Bupropion quitting rate in our study fell between findings from two RCTs that were conducted in 2005 and 2007 (16% and 36%) [4, 28]. It is not surprising to see lower quit rates when compared to RCTs as RCT participants are usually under rigorously controlled settings and require frequent clinic follow ups. An interesting finding here was that those who were prescribed more than one medication within 3-month treatment window had the lowest quit rate compared to mono-therapy. This result was also similar in the logistic regression model after adjusting for all other possible confounders, those who belonged to the combination group had the lowest chance of quitting at month 3 (OR=0.38, 95% CI=0.15 – 1.00). This indicates that if an individual was not successful in quitting smoking with the product provided to him, it is very likely that adding on more medications or switching to other treatment alternatives will not help. Abstinence observed at the 12^{th} week is the best way to assess drug treatment effect because most of the medications are prescribed for 12 weeks. Stronger conclusions could be made if smoking status was assessed at the 12^{th} week mark following prescription date.

Abstinence from smoking at year 1 is also important, as it allows the assessment of a sustained quitting effect. In our cohort, among the 235 quitters at 12th week, 170 (75.22%) of them were still not smoking at year 1. The percentage was high which indicates that if schizophrenic smokers could make it through week 12, chances are high that they would not go back to the smoking behavior at one year. This finding, however, was based on those who got prescribed Varenicline or NRT. Results could be found in Table 4 for those whose index medication was Bupropion or combination group. They were not included in further analysis because the sample size was too small to make robust conclusions. Among the 4 quitters at 12th week for Bupropion, all of them also reported not smoking at year 1 (100%); on the other hand, among the 5 quitters at 12th week for combination treatment, only one of them reported not smoking at year 1 (20%). The sample size in both Bupropion and combination treatment group precludes us from making generalizable conclusions.

Findings also demonstrate that regardless of quitting at the 12th week, overall abstinence rate at one year among all patients prescribed cessation medications was 17.20% with Varenicline again being the highest (20.07%), followed by combination (16.87%), NRT (16.09%), and Bupropion being the lowest (14.29%). To our knowledge, no previous retrospective studies have been conducted specifically among schizophrenic patients. RCTs for this minority population usually were conducted in a short term timeline so none tracked patients' smoking status up to year 1. We could only compare our cessation rate with that in the general population. Quitting rate at one year was 36.7% and 28.0% for Varenicline from 2007 and 2008 RCTs [61], 28.0% and 35% for Bupropion from 2003 and 2007 RCTs [87, 88], and 25% for NRT from a 2002 RCT [89]. All of these rates were higher as compared to our finding, but this is expected as these rates were among smokers without psychiatric illnesses. Furthermore, most of

studies included regular follow ups with telephone calls to remind RCT participants scheduling appointments.

Our results showed that patients who received smoking counseling during one year prior to index date were less likely to quit smoking compared to those who received the counseling message. Both short term (14.51% vs. 22.13%) and long term abstinence rates (73.74% vs. 76.38% for continuous abstinence and 14.50% vs. 19.90% at year 1) were lower among those who received counseling. Similarly, when adjusting for other possible confounders in the multiple logistic regression, this factor still came out significant in model 1a for quitting at 12^{th} week (OR=0.67, 95% CI=0.49 – 0.92). This finding was not expected because evidence is strong that interventions can considerably improve cessation rates [79]. Smoking cessation interventions with both pharmacological and behavioral intervention are more effective than pharmacological or behavioral interventions alone [90]. One possible reason to explain our finding could be that patients who received the counseling were also more severe smokers and were more addicted to nicotine; therefore, quitting for them was a bigger challenge. Though we attempted to control for addiction level in the models, the measure might not be sensitive enough because those who were prescribed Bupropion or Varenicline were all categorized as high nicotine addiction level. Another possible reason could be that the training of smoking counseling for healthcare providers was not mature enough. Hospitals or clinics should provide their healthcare employees with more practical materials or educational brochures to improve their skills regarding anti-smoking messages. Smoking counseling has been shown to be the most cost effective service, provision of advice and support from healthcare professionals could translate into a substantial public health benefit if consistently provided [83]. When delivering smoking counseling, healthcare providers should follow the current U.S. Public Health Service (USPHS) Clinical Practice Guideline to employ the 5 A's: ask the patient about tobacco use, advise users to quit,

assess willingness to quit, assist in the quit attempt, and arrange for follow-up [82]. In previous studies, counseling was mostly performed by physicians or nurses, at the time of a primary care visit. A frequently overlooked opportunity for counseling occurs when patients fill prescriptions for tobacco cessation. Satisfaction for pharmacists counseling seemed high from smokers [86]. Schizophrenic patients, however, may need more tailored approaches for counseling that should be evaluated in future studies to achieve a successful cessation outcome.

In our first logistic regression model, patients at the West region of U.S. were more likely to quit smoking (OR=2.18, CI=1.39 – 3.41). This may be a result of the different law restrictions regarding smoking across the nation. According to a previous study, California and Utah are the top two supportive states toward smoke-free laws [91]. Most indoor California workplaces, clubs/bars and gaming rooms were mandated to be smoke-free. The comprehensive California Tobacco Control Program has placed particular emphasis on changing social norms about smoking as a means to accomplish its smoke-free goal [92]. This program is unique in the nation with respect to its duration and level of funding. Fewer people will smoke in a society where smoking is not viewed as an acceptable activity.

In our model 1a, we found that as one year increase in age, chances of successful short term quitting increases by 2% (OR=1.02, 95% CI=1.01 – 1.03). Our finding is consistent with the study conducted by Lee et al. among general population [93]. This seems reasonable since older smokers have more medical conditions and they tend to be more concerned about their health than younger aged smokers. They understand the harmful effects of smoking as they get older and may be more serious about quitting.

In our sustained abstinence model (model 1b), the only predictor we found was the second exposure to cessation medications. Among those who quit at week 12, if there was a

second exposure between week 16 to one year, then they were less likely to quit at year 1 (OR=0.26, 95% CI=0.13 – 0.55). There are two possibilities for patients to receive cessation medication prescriptions during this period; either the medication was used as a treatment for preventing smoking relapse, or it was used because patients went back to their previous smoking behavior habit. Articles below provide some examples for extending cessation medications use for smoking relapse prevention. Tonstad et al. conducted a study in 2006 [94], they first recruited 1,927 smokers and treated with open label Varenicline for 12 weeks, after that, they subsequently continued the study into a randomized trial. A total of 1,210 who did not smoke after the first phase were enrolled in the second stage. One mg Varenicline or placebo was provided to patients for an additional 12 weeks and they found that continuous abstinence rates were significantly higher for those who were on Varenicline: for weeks 13 - 24 (70.5% vs. 49.6%; OR=2.48, 95% CI= 1.95-3.16 and for weeks 13 - 52 (43.6% vs. 36.9%, OR=1.34, 95% CI=1.06-1.69). A similar study conducted by Hurt et al. first enrolled smokers (N = 784) who were interested in stopping smoking in a 7-week, open-label Bupropion phase [95]. At the end of treatment, abstinent subjects (N = 429) were then subsequently randomized to active Bupropion or placebo through week 52 for preventing relapse. At the end of drug treatment, they found those who were on Bupropion had higher rates of smoking abstinence as compared to placebo (p=0.008). Though we did not include Bupropion in our analysis, this explains cessation medication used for preventing smoking relapse is not uncommon. Both studies demonstrated a significant long-term relapse prevention effects, however, the studies population included were generally healthy samples and not patients with psychiatric illnesses. If the second exposure were used for smoking prevention, then our results are inconsistent with their findings. This could be due to the adherence issues. Schizophrenic patients usually are on multiple medications and they

might not adhere to daily cessation medication regimen that is required taking for a longer term [96]. This could potentially explain why those who had the second exposure were more likely to smoke at 1 year: without taking the medication on a regular basis, treatment for preventing smoking relapse will result in failure. Another potential explanation could be that the exposure of second medication was because they relapsed to the original smoking behavior. For those who did not have a firm determination to quit, no matter how many times they got prescribed cessation medication, chances of sustained quitting may be low.

For our one year quitting (regardless of smoking status at week 12) model, we found a strong and only predictor - those who did not smoke at week 12 were also more likely to be abstinent at year 1 (OR=56.49, 95% CI=36.48 – 87.49). This indicates that if schizophrenic smokers could make it through week 12, chances are high that they would not go back to the smoking behavior. However, in preventing from smoking relapse, there is still a need for consistent counseling and monitoring by healthcare providers to former smokers with compliments on their persistence towards the non-smoking behavior.

Strengths and Limitations

The limitations in this study are mainly related to using EMR data: (1) we could not track if patients picked up the medication at a pharmacy. Medication data were identified by physician orders, which did not guarantee that the patients actually filled the prescription. (2) We are not certain how compliant the patients were. Unlike chronic medications, cessation products are usually for a short term use, so compliance should not be a significant problem [96]. (3) Some important variables were with missing information, for example, the stop dates of medications were sometimes missing and smoking status was not recorded regularly. With missing values, it is difficult to generalize our findings. Furthermore, information was not recorded in GE data for

some possible confounders like education level and nicotine addiction level (or how many cigarettes they smoke per day). We tried to infer nicotine addiction level from the NRT dosages they were prescribed but we would not be able to do so for those who were on Bupropion SR or Varenicline because the doses are fixed. Those who got Bupropion SR (Zyban) or Varenicline were assumed to have a high addiction as they did not go for the choice of easily accessible NRT. We might also underestimate the percentage of those on NRT and Bupropion. NRT usage might be under estimated because majority of products are over the counter. Smokers might not mention that information to their doctors if not being asked; therefore, it would not be recorded in GE EMR. As previously discussed, Bupropion (Zyban®) might be under estimated: depression is a common comorbid condition and physicians are more likely to prescribe anti-depressant Bupropion (Wellbutrin®) which is most likely being covered compared to Zyban®.

Despite the limitations above, the population distribution in GE EMR is very similar with the US population and thus is representativeness of outpatient practice. It is also rich in clinical information including vital signs, laboratory results, medication list entries or prescriptions, and diagnoses or problems. With proper smoking status and smoking cessation medications (including NRT OTCs), it was considered an appropriate database for our research questions. Our study is the first observational study to examine effectiveness of smoking cessation medications among schizophrenic smokers. Previous works were all randomized clinical trials in nature with small sample size and strict inclusion criteria.

CONCLUSIONS

This was the first retrospective study to examine smoking abstinence at both short and long term among schizophrenic smokers. Abstinence rate was approximately 18.02% at week 12 and 17.20% at year 1. Among those who quit at 12^{th} week, about 75.22% of the quitting effect

sustained at 1 year. After 12 weeks of cessation treatment, we found there were no statistically differences in quitting between medications. However, those who were on more than one medication had slightly lower chances of quitting with the effect almost reached the significance level. After one year of the exposure, no medication differences were observed either, and this was the same for the continuous abstinence. Other predictors we found that were associated with quitting included being older, white, whose residential area was in the west part of U.S., and without smoking counseling. Patients who reported not smoking at week 12 and who did not receive cessation medication prescriptions during week 16 to year 1 were more likely to be abstinent from smoking at year 1. Predictors identified in this study should be considered when designing smoking cessation interventions. Further, this minority population may need more tailored approaches to achieve a successful cessation outcome.

MANUSCRIPT 2

Comparison of Cardiovascular Risks following Smoking Cessation Treatments Using Varenicline vs. NRT among Schizophrenic Smokers

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INTRODUCTION

Smoking is a serious public health problem. Tobacco use causes approximately 443,000 premature deaths annually in the United States (US) [1, 2] and 5.4 million worldwide [3]. The annual economic losses to the US society are estimated at $193 billion with $96 billion in direct medical costs [1]. As compared to the general population, schizophrenic patients have much higher smoking rates: 72% - 90% vs. 23% [4]. Schizophrenic patients also tend to be heavy smokers [5], to have much lower smoking cessation rates and higher nicotine dependence level [6, 7]. The high prevalence can be possibly due to the self-medication effect of tobacco [22]. Tobacco may be used to alleviate some of the symptoms in schizophrenia and the side-effects of antipsychotic medications [23]. Quitting smoking may worsen their psychiatric symptoms, therefore, these patients cannot and do not want to quit their tobacco use [25]. People with schizophrenia die on average 10 years earlier than people in the general population, and age-adjusted rates of death because of cardiac and pulmonary disease are significantly elevated in this population, suggesting that tobacco use is an important cause of the excess mortality observed in schizophrenia [28].

Smoking cessation is highly recommended by public health department of various organizations and several smoking intervention strategies are available for smokers. During the 1990s, a variety of pharmaceutical cessation aids became available, which include nicotine replacement therapy (NRT) and the antidepressant Bupropion SR [8]. Even more recent, Varenicline was approved as an aid to smoking cessation [9]. The FDA suggested dosage regimen is usually for 12 weeks for cessation pharmacotherapies [31].

Cardiovascular disease is an important cause of morbidity and mortality among tobacco users. The long-term cardiovascular benefits of smoking cessation are well established [29, 58].

Many pathophysiological changes caused by smoking can be reversed or improved by smoking cessation. A systematic review in patients with CHD showed that smoking cessation reduced the relative risk of death by 36% and risk of re-infarction by 32% compared with continuing smokers [29]. Even though smoking cessation is associated with substantial health benefits, weight gain after quitting is commonly cited [10]. In the U.S., it is estimated that 80% of people who quit smoking gain weight [11]. The average weight gain in people who sustained quitting for eight years was about 9kg, with 42% of people gaining even over 10kg. This weight gain can have health consequences, like the development of diabetes after cessation [11]. Yeh et al. [63] found that in the first 3 years of follow-up, compared with non-smokers, the hazard ratios of diabetes among former smokers, new quitters, and continuing smokers were 1.22 (95% CI: 0.99 – 1.50), 1.73 (95% CI: 1.19 – 2.53), and 1.31 (95% CI: 1.04 – 1.65), respectively. This indicates that smoking cessation leads to a higher short-term diabetes risk. Furthermore, in other studies, NRT has shown to reduce sensitivity to insulin and may aggravate or precipitate diabetes [56].

In addition to diabetes, the risk of hypertension may increase after quitting smoking. Janzon et al. [12] included a total of 2,381 female never smokers and 1,550 female smokers in a 9-year follow up study. At the end, 388 of the 1,550 smokers had quit smoking. They found that after 9-years of follow up, mean weight gain was 7.6 ± 6.1, 3.2 ± 5.8 and 3.7 ± 5.2 kg, respectively, in quitters, continuing smokers and never smokers ($P < 0.001$). In women without blood pressure medication treatment, mean SBP increase was 20.9 ± 16.8, 19.1 ± 15.8 and 16.1 ± 16.3 mmHg, respectively ($P < 0.001$). Mean DBP increase was 6.2 ± 8.7, 5.7 ± 9.3 and 3.1 ± 8.0 mmHg, respectively ($P < 0.001$) (quitters, continuing smokers and never smokers). After adjustments for potential confounders, the differences in SBP and DBP increase were attenuated, but remained significant. Incidence of hypertension (≧ 160/95 mmHg or anti-hypertension

treatment) was significantly higher in quitters (adjusted OR=1.8, 95% CI: 1.4–2.5), and continuing smokers (adjusted OR=1.3, 95% CI: 1.07–1.6) when compared with never smokers. Another study conducted by Terace et al. [64] also reported a similar finding. They found more quitters (35%) became hypertensive than non quitters (27%, $p<0.01$) after 7 years of follow up, although the two groups (quitters and non quitters) had similar blood pressure levels at baseline. The increased blood pressure finding or the excess incidence of hypertension in quitters might be due to the effect of weight gain after cessation.

For schizophrenic patients, these risks can be even more concerning because the antipsychotic medications they are taking increases their likelihood of developing metabolic syndromes. Second generation antipsychotics (SGAs) have become the drugs of choice for treating schizophrenic patients in many countries including the United States [47] because they are believed to be more effective and safer than conventional antipsychotics [46]. With the weight gain from smoking cessation and SGAs combined, the risks of quitting smoking specifically among schizophrenic patients have to be evaluated. Furthermore, Bupropion has been shown to inhibit enzyme CYP2D6 and would reduce the clearance of drugs metabolized by it (e.g., antipsychotics or tricyclic antidepressants) [28]. Therefore, risks of developing metabolic side effects would be even higher for patients receiving Bupropion.

Aside from that, cessation medications that receive priority review have limited safety data at the time of approval. Many studies for Varenicline before 2010 showed that there were very few side effects and no clinically significant drug–drug interactions were observed [65]. However, some studies and reviews after 2010 actually showed Varenicline increases the chances of developing cardiovascular diseases. A review and meta-analysis [58] analyzed data from 14 double blind randomized controlled trials involving 8,216 participants. The trials ranged

in duration from 7 to 52 weeks. Varenicline was associated with a significantly increased risk of serious adverse cardiovascular events compared with placebo (1.06% [52/4908] in Varenicline vs. 0.82% [27/3308] in placebo group; OR=1.72, 95% CI= 1.09–2.71). A report even showed that a 30-year old smoker without previous history of coronary artery disease developed acute thrombotic occlusion and acute coronary syndrome after Varenicline exposure [66]. The product label was subsequently updated in December, 2012, according to FDA's request: "Post marketing reports of myocardial infarction and cerebrovascular accidents including ischemic and hemorrhagic events have been reported in patients taking Varenicline [58]."

Studies have examined the effect of quitting in preventing new onset of cardiovascular diseases among general population but not specifically among schizophrenic smokers. The comparative risks between cessation medications in this high risk population have yet to be evaluated. The benefits of quitting among schizophrenic patients should be carefully evaluated as tobacco may be used to alleviate some of the schizophrenic symptoms. There is also a need to evaluate how different smoking cessation strategies can modify these risks among schizophrenic patients given the medication regimens they already take.

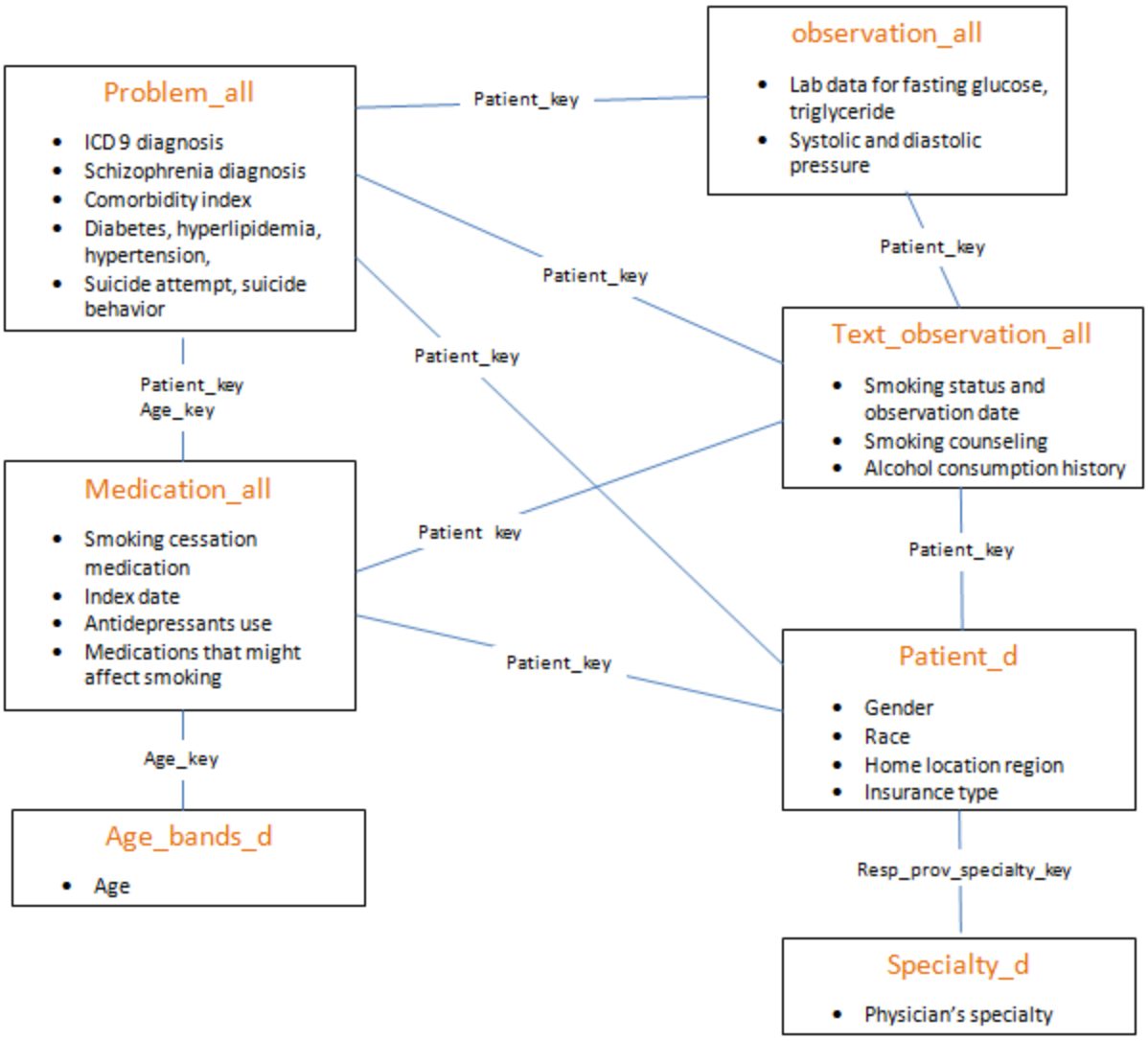
METHODS

Data source

The data used for this study were extracted from the General Electric Centricity Electronic Medical Record (GE EMR) research database. The Centricity EMR database is used by more than 20,000 clinicians and contains longitudinal ambulatory electronic health data for more than 7.4 million patients, including demographic data, vital signs, laboratory orders and results, medication list entries and prescriptions, and diagnoses or problems. A variety of practice types are represented in the database, ranging from solo primary care practitioners to community

clinics, academic medical centers, and large integrated delivery networks [73]. Both medications and prescriptions are documented in the database. Medications may include a broader list of all medications that a patient is taking including over the counter medications, herbal remedies and medications prescribed by a provider that may be out of the EMR network. On the other hand, prescriptions are medications that have been prescribed by the responsible provider of this patient within the EMR. As some forms of NRTs are OTCs and cannot be captured in most of the claims data, the GE EMR dataset is an appropriate tool for our data analysis. Moreover, the availability of smoking status information makes it the ideal clinical database to be used. Data are collected centrally and go through a quality-control process to remove invalid values [74]. One study using data in 2005 showed that the population distribution in the GE EMR dataset is very similar to that in the US population. The proportion of patients aged 18 to 64 years in the GE EMR population is 63%, which is similar to that in the US general population. Furthermore, of the patients in the GE EMR whose race is documented, 79% are white and 15% black, compared with 81% white and 13% black in the US population [74]. GE data set has been widely used in studying smoking, for example, Fox et al. assessed effectiveness of different statins among diabetes mellitus patients with smoking status as one of the covariates [75]. GE data consists of several different files that give different information, for example, "problem file" has information with ICD9 diagnosis, "text observation file" has information with smoking status, or "patient_d_file" has patients' demographics information. The protocol to linking the different files together is detailed in Figure 1 below.

Figure 1: Linkage between GE data files



Study population

We included patients who were enrolled between 12/13/1995 to 10/31/2011. Patients aged below 18 years old or those who received Wellbutrin® (Bupropion SR) for depression 6 months prior to index date were excluded from this study. From the GE healthcare EMR databases, we identified patients with a diagnosis of schizophrenia or schizoaffective disorder (ICD-9 code 295.00-295.99) [76].

Numerous studies linked atypical and not traditional antipsychotics to the development of metabolic syndromes in patients with schizophrenia [97], therefore, we would only include those

who had exposure of atypical antipsychotics 6 months prior to index date in this cohort. The objective was to assess the new onset of cardiovascular diseases' risk factors; therefore, patients who already had diagnosis of diabetes, hyperlipidemia or hypertension prior to index date were excluded from the cohort.

Exclusion criteria

(1) Was prescribed more than one medication the same day as their index medication

(2) Was not prescribed atypical antipsychotics 6 months prior to index date

(3) Already had diabetes, hyperlipidemia, or hypertension prior to index date

After identifying the population, we constructed a series of new-user cohort of patients who had newly initiating use of smoking cessation medications. Only the first exposure to each of the smoking cessation medication was examined so we could be sure the quitting is not affected by the previous cessation product they took. The first day of being prescribed smoking cessation medication was defined as the index date.

Definitions of outcome – cardiovascular risks (elevated glucose, cholesterol, and blood pressure level)

Cardiovascular disease is a long term outcome. Based on the National Cholesterol Education Program (NCEP), some identified risk factors for developing cardiovascular disease include: (1) elevated fasting glucose (≧110 mg/dl), (2) elevated triglycerides (≧150 mg/dl), and (3) blood pressure level (≧130/ ≧85 mm Hg) [59]. These metabolic syndromes can be assessed in a short term study. According to a smoking cessation Varenicline RCT, researchers requested

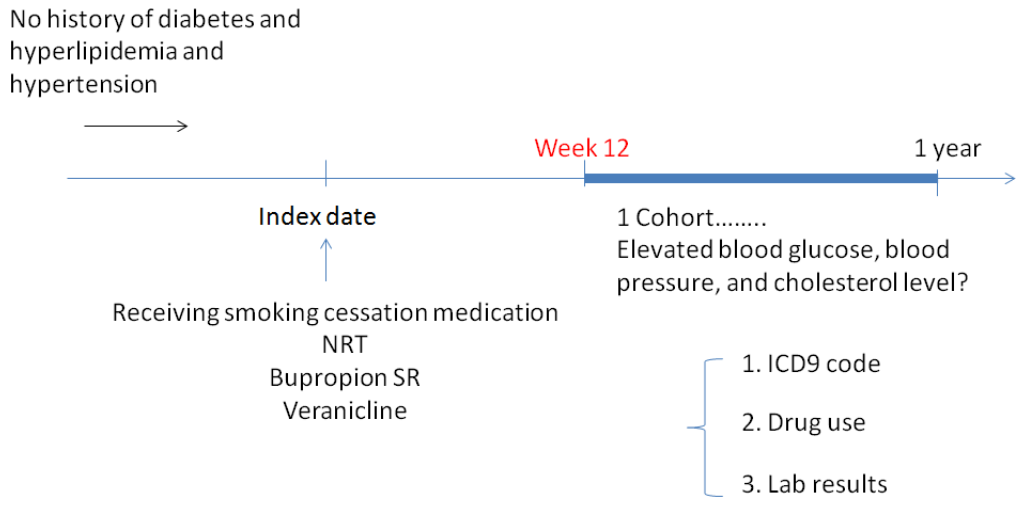
that participants come back for physical examination like ECG or blood test at week 12 and 52 [62], which means the authors believed cessation medications may have some effects on blood results starting from week 12. Therefore, in our study, we examined "problem file", "medication file", and "observation file" (which has their information for diagnoses, medications, and lab data) 12 weeks onwards index date (to be sure our criteria is similar to that of RCTs) up to one year. Patients were considered to have elevated glucose level if they have an ICD9 code 250 [98] or receiving an anti-diabetic agent (ie, insulin, sulfonylureas, biguanides, thiazolidinediones, *a*-glucosidase inhibitors, or meglitinides, etc) or with fasting glucose blood test results ≧ 110 mg/dL [59] 12 weeks onwards index date [99]. Similarly, the elevation of cholesterol level were identified by an ICD9 code 272 [100] or receiving an anti-hyperlipidemia agent [97], or with a triglyceride level ≧150 mg/dl [59, 101]. For both blood glucose and cholesterol, the occurrence of drug therapy was considered sufficient to identify an outcome because these drugs are almost exclusively used for the primary indication. On the other hand, the elevation of blood pressure was identified only by ICD9 codes 401 – 405 [98] or by blood pressure level ≧ 130/85 mmHg [59]. A prescription for antihypertensive was not considered as a reliable indicator because of the large number of secondary indications for these agents (eg, β-blockers for antipsychotic-induced akathisia) [97].

Analysis Plan

In order to examine if there are differences in cessation medication prescription type with patient characteristics, we first carried out descriptive statistics and chi-square analyses. A Cox proportional hazards model was then constructed and we studied the factors associated with elevated glucose, cholesterol, and blood pressure level developed over the course of follow-up. Observation began 12 weeks after index day and continued until one year after the treatment

exposure. At the end of one year window, patients would either develop the outcome or be censored. They were censored if they satisfied any of the three conditions below: (1) the last day the index medication being prescribed, (2) switching over to (or adding on) another smoking cessation medication and (3) did not develop the outcome when they reached the one year follow up timeline. To explain (1) in more detail: start and stop date of the medication were recorded in GE data. Though lots of stop dates were missing, the information is still very useful. The total duration (t=months) was calculated as [the date of the endpoint (the date of the outcome or the date being censored) – (index date) – 83] divided by 30. The follow up period was from week 12 (84 days after the index medication) and up to one year and that's why we subtracted 83 here. Please see Figure 2 for the objective analysis plan.

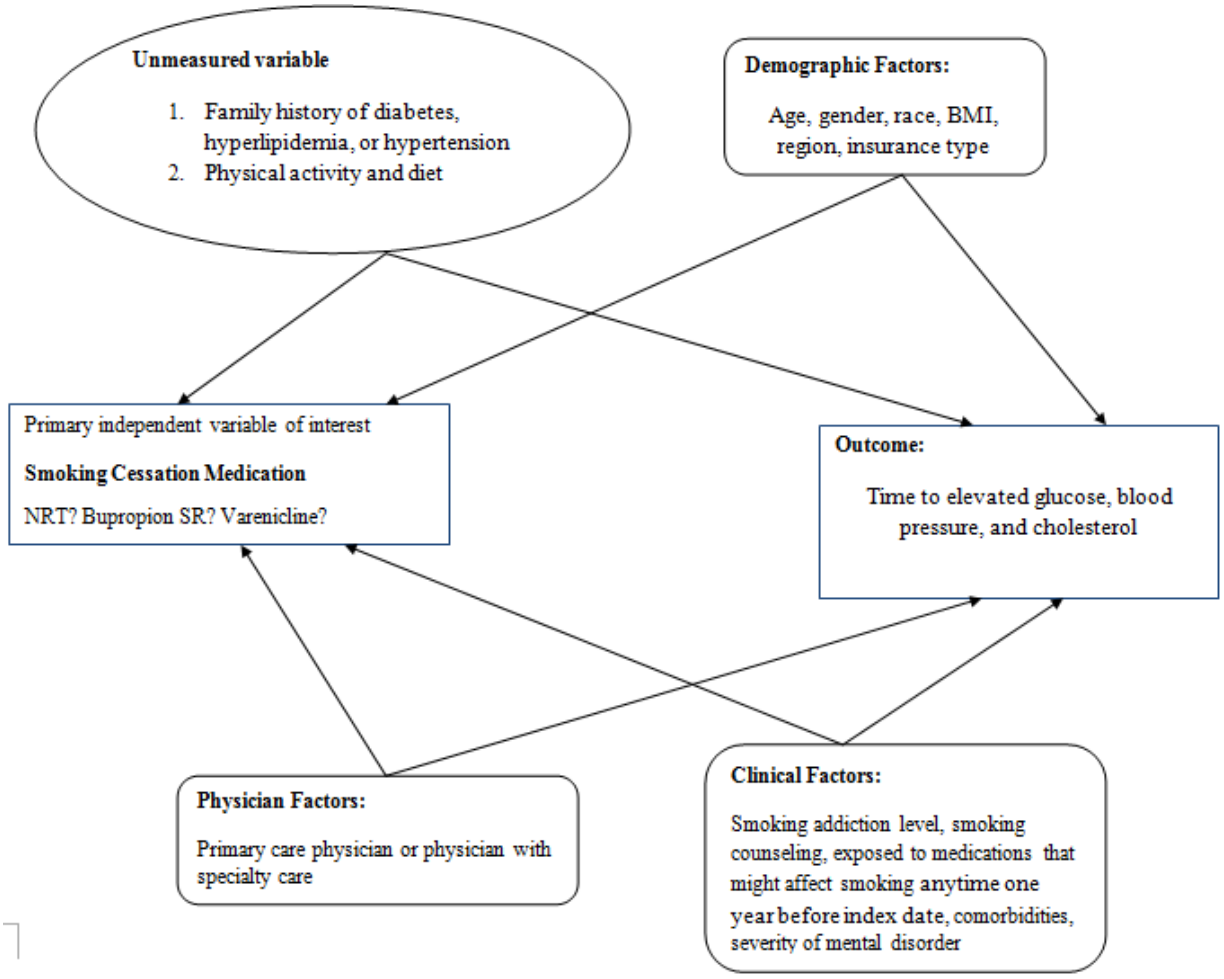
Figure 2: Analysis plan



The primary outcome of interest in this Cox regression model was the cessation medication they received (NRT, Bupropion SR or Varenicline). Other potential confounders were included in Cox proportional hazards model as well, which included: age, race, gender, region (Midwest, Northeast, South, West), BMI (normal, over-weight or obese) [102], payment

type (government or non government insurance), specialty group (primary care, specialty care), nicotine addiction level, received smoking counseling, exposure to medications that might affect their smoking status (nortriptyline, buspirone, clonidine, naltrexone, mecamylamine, or rimonabant) anytime one year before index date, comorbidity index, and severity of mental disorder (having antipsychotic injections anytime one year before index date). We tried to infer nicotine addiction level from the NRT dosages they got. If their starting dose for nicotine patch was 21mg/day or nicotine gum 4mg/piece then they were classified as high nicotine addiction; on the other hand, if their starting dose for nicotine patch was 14mg/day or 7mg/day, or nicotine gum 2mg/piece, then they were classified as low nicotine addiction. However, we would not be able to do so for those who were on Varenicline because the dose is fixed. Those who got Varenicline were assumed to have a high addiction as they did not go for the choice of easily accessible NRT. Family history of those diseases, physical activities and diet were not recorded in GE data so those could be possible unmeasured confounding factors. Figure 3 below shows the conceptual model for time to elevated glucose, cholesterol, and blood pressure.

Figure 3. Conceptual model for time to elevated glucose, cholesterol, and blood pressure



There are some assumptions that we have to satisfy for conducting the survival analysis. The proportional hazard assumption was checked for all the independent variables one at a time in the model by using Schoenfield test. If our primary independent variable (cessation medication) were to violate the assumption, time dependent variable would then be created using heavyside function to adjust for time in the analysis. On the other hand, if other independent variables that were to violate the assumption, we would carry out further analyses with those variables being stratified. We first did a univariate Cox regression analysis for each of the independent variable and included variables with $p<0.2$ or important counfounders in the multivariate Cox regression model. Demographic variables like age, gender or race, were included in the multivariate model regardless of the significance levels in the univariate analysis.

Interaction terms between the main predictor and other independent variables were tested as well. Hazard ratio (HR) and its 95% CI were used to present the results for the final Cox PH regression model.

Sensitivity analysis (1) – applying different follow up periods

A shorter follow up period was performed: from index date up to 12 weeks. This was to examine if the results remained robust when applying different timelines.

Sensitivity analysis (2) – sub-sample analysis

The previous analysis was conducted among all the patients who met the inclusion criteria. We believe that quitting smoking or not would have a significant effect on the glucose, cholesterol and blood pressure level because of weight gain after cessation. As shown in the previous survival model, quitting smoking or not was not one of the independent variables, but the cessation medication was. Abstinence is the effect of cessation medication so if we are to control that, we are like controlling for part of the medication's effect, the effect of medication will therefore be attenuated. To avoid that, we did two sub sample analyses: one for those who quit at year 1 and the other one for those who did not.

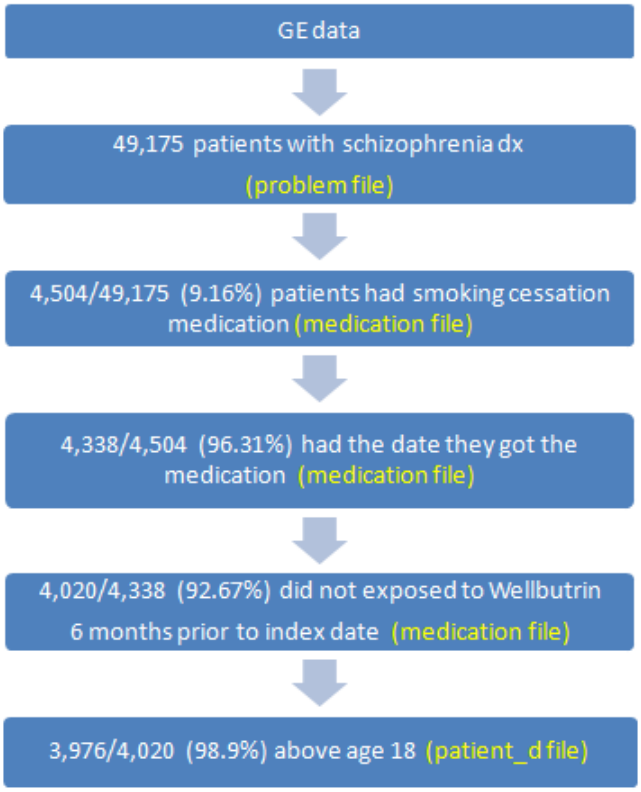
RESULTS

Cohort distribution

From the inception of GE data, we found there are a total of 49,175 patients had at least one diagnosis of schizophrenia or schizoaffective disorder (from December 1995 to October 2011). About 10% of them got at least one cessation medication at any point (n=4,504, 9.16%). Most of the dates they received the medication were recorded (n=4338, 96.31%) and those

without the dates were dropped. To meet our study exclusion criteria "individual aged below 18 years old" or "those who received antidepressants Bupropion (Wellbutrin®) at any point 6 months prior to index date" were also dropped from our study cohort. This brought us down to a total of 3,976 patients. Please see Figure 4 below for how we identified our population.

Figure 4. Identification of our population



After applying more exclusion criteria: (1) was prescribed more than one medication the same day as their index medication, (2) were not prescribed atypical antipsychotics 6 months prior to index date, and (3) those already had diabetes, hyperlipidemia, or hypertension prior to index date, the cohort came down from 3,976 to 580. Please see Table 1 for detailed characteristics.

Slightly more than half were of male gender (n=307, 52.93%), about forty percent were whites (n=238, 41.03%), and majority were with high nicotine addiction level (n=477, 82.24%).

About half of the cohort (n=255, 43.97%) had a normal BMI as they did not have the diagnosis of diabetes, hypertension, or hyperlipidemia. Almost all of them had stable mental state as only 4.14% (n=24) of the cohort had antipsychotics in the injection form at any point 1 year prior to index date. Slightly more than half (n=286, 51.25%) of the cessation medication users were under Medicare or Medicaid coverage. The mean age of the cohort was 40.56 years old (± SD: 11.68) with a minimum of 18 and a maximum of age 78. Most of the cessation medications were prescribed by their primary care physicians (n=562, 96.90%) and about forty percent of the patients had received smoking counseling from their healthcare providers anytime one year prior to index date (n=231, 39.83%). Please see Table 1 for patients' characteristics by the prescribed cessation medication types.

As it shows in the Table 1, NRT (n=413, 71.21%) was used more commonly compared to Varenicline (n=167, 28.79%). Bupropion was not included in the analysis because of the low sample size: only 10 individuals were prescribed Bupropion after applying the inclusion/exclusion criteria.

Among the 580 patients, a total of 276 (47.59%) had elevated glucose/cholesterol/blood pressure from week 12 up to one year after the cessation medication exposure. The association between all the independent variables and the outcome can also be found in Table 2.

Predictors for developing elevated glucose/cholesterol/blood pressure during 1-year follow up time period

All the independent variables in the model met Schoenfield assumption so there is no need for further adjustments for our model. No interactions were found between the cessation medications and other independent variables using chunck test. The model with all the

interaction terms was not statistically different from the model without the interactions: likelihood ratio difference between the two models (all independent variables and all independent variables + interactions) was 19.619, giving a non significant p-value between 0.1 – 0.2 at 15 degrees of freedom.

Males (HR=1.47, 95% CI=1.14 –1.89), obese adults (HR=1.63, 95% CI=1.24 –2.15), and those with high comorbidity indices (HR=1.17, 95% CI=1.08 –1.26) had higher risks in developing elevated glucose/cholesterol/blood pressure. We found that those whose index cessation mediation was NRT had lower risks of developing cardiovascular risk factors (HR=0.71, 95% CI=0.54 –0.94). Other significant characteristics that we found significantly affect metabolic syndromes included being male gender, obesity, and with higher comorbidity index. Please see Table 3 for our multivariate PH regression result.

Table 1. Overall baseline characteristics of the study cohort and numbers (percentages) within each cessation medication

Characteristics	Overall cohort Total Frequency (Percentage)	Varenicline N=167 (28.79)	NRT N=413 (71.21)	p-values
Demographics				
Sex				
Female	273 (47.07)	87 (52.10)	186 (45.04)	0.1230
Male	307 (52.93)	80 (47.90)	227 (54.96)	
Age (years)				0.0570
Race				
Blacks	74 (12.76)	14 (8.38)	60 (14.53)	0.0982
Whites	238 (41.03)	68 (40.72)	170 (41.16)	
All others	268 (46.21)	85 (50.90)	183 (44.31)	
Region				
Midwest	191 (32.93)	56 (33.73)	134 (32.45)	
Northeast	190 (32.76)	36 (21.69)	154 (37.29)	**0.0009***
South	90 (15.52)	31 (18.67)	59 (14.29)	
West	109 (18.79)	43 (25.90)	66 (15.98)	
BMI				
Normal (BMI<25)	255 (43.97)	70 (41.92)	185 (44.79)	0.8166
Overweight (25<=BMI<30)	123 (21.21)	37 (22.16)	86 (20.82)	
Obesity (BMI>=30)	202 (34.83)	60 (35.93)	142 (34.38)	
Insurance				
Not Medicare/Medicaid	272 (48.75)	77 (48.43)	195 (48.87)	0.9245
Medicare or Medicaid	286 (51.25)	82 (51.57)	204 (51.13)	
Clinical factors				
Comorbidty Index				**0.0100***
Had antipsychotic injectables 1 year prior to index date				
No	556 (95.86)	162 (97.01)	394 (95.40)	0.3791
Yes	24 (4.14)	5 (2.99)	19 (4.60)	
Smoking Cessation Related				
Addicted to nicotine				**<0.0001***
No	103 (17.76)	0 (0.0)	103 (24.94)	

Yes	477 (82.24)	167 (100.0)	310 (75.06)	
Cessation Rx given by specialty care physician?				
No	562 (96.90)	156 (93.41)	406 (98.31)	**0.0021***
Yes	18 (3.10)	11 (6.59)	7 (1.69)	
Received any medication that might affect smoking status anytime 1 year prior to index date				
No	541 (93.28)	157 (94.01)	384 (92.98)	0.6526
Yes	39 (6.72)	10 (5.99)	29 (7.02)	
Smoking counseling received anytime one year prior to index date				
No	349 (60.17)	101 (60.48)	248 (60.05)	0.9236
Yes	231 (39.83)	66 (39.52)	165 (39.95)	
Total cohort=580; * p≤0.05				

Table 2. Characteristics of patients developing elevated glucose/cholesterol/blood pressure during 1-year follow up

Characteristics	Elevated glucose/cholesterol/blood pressure (n=276, 47.59%)	
	Number (%)	Hazard ratio p-values
Demographics		
Sex		
Female	117 (42.86%)	**0.0186***
Male	159 (51.79%)	
Age (years)		0.7996
Race		
Blacks	32 (43.24%)	0.4721
Whites	120 (50.42%)	
All others	124 (46.27%)	
Region		
Midwest	93 (48.95%)	
Northeast	94 (49.47%)	0.6242
South	41 (45.56%)	
West	47 (43.12%)	
BMI		
Normal (BMI<25)	109 (42.75%)	**0.0070***
Overweight (25<=BMI<30)	54 (43.90%)	
Obesity (BMI>=30)	113 (55.94%)	
Insurance		
Not Medicare/Medicaid	125 (45.96%)	0.3764
Medicare or Medicaid	141 (49.30%)	
Clinical factors		
Comorbidty Index		**0.0007***
Had antipsychotic injectables 1 year prior to index date		
No	268 (48.20%)	**0.1565***
Yes	8 (33.33%)	
Smoking Cessation Related		

Addicted to nicotine		
No	44 (42.72%)	0.3965
Yes	232 (48.64%)	
Cessation Medication		
Varenicline	90 (53.89%)	**0.0837***
NRT	186 (45.04%)	
Cessation Rx given by specialty care physician?		
No	270 (48.04%)	0.2499
Yes	6 (33.33%)	
Received any medication that might affect smoking status anytime 1 year prior to index date		
No	262 (48.43%)	0.2049
Yes	14 (35.90%)	
Smoking counseling received anytime one year prior to index date		
No	169 (48.42%)	0.6290
Yes	107 (46.32%)	
Total cohort=580; * p≤0.05		

Table 3. Predictors of developing elevated glucose/cholesterol/blood pressure during 1-year follow up among schizophrenic smokers who were prescribed cessation medications

Characteristics	Elevated glucose/cholesterol/blood pressure (n=276, 47.59%)	
	Unadjusted HRs	Adjusted HRs
Demographics		
Sex		
Female	Reference	Reference
Male	**1.34 (1.05 –1.70)***	**1.47 (1.14 –1.89)***
Age (years)	1.01 (0.99 –1.02)	1.01 (0.99 –1.02)
Race		
Blacks	Reference	Reference
Whites	1.21 (0.82 –1.78)	1.26 (0.82 –1.92)
All others	1.05 (0.72 –1.55)	1.05 (0.69 –1.61)
Region		
Midwest	Reference	Reference
Northeast	1.03 (0.78 –1.37)	0.98 (0.72 –1.35)
South	0.89 (0.62 –1.28)	0.79 (0.53 –1.19)
West	0.84 (0.60 –1.20)	0.76 (0.52 –1.10)
BMI		
Normal (BMI<25)	Reference	Reference
Overweight (25<=BMI<30)	0.99 (0.72 –1.38)	0.98 (0.70 –1.38)
Obesity (BMI>=30)	**1.47 (1.13 –1.91)***	**1.63 (1.24 –2.15)***
Insurance		
Not Medicare/Medicaid	Reference	Reference
Medicare or Medicaid	1.12 (0.88 –1.42)	1.11 (0.86 –1.42)
Clinical factors		
Comorbidty Index	**1.13 (1.06 –1.21)***	**1.17 (1.08 –1.26)***
Had antipsychotic injectables 1 year prior to index date		
No	Reference	Reference
Yes	0.61 (0.30 –1.22)	0.53 (0.26 –1.07)
Smoking Cessation Related		
Addicted to nicotine		
No	Reference	Reference

Yes	1.15 (0.84 –1.59)	1.09 (0.77 –1.56)
Cessation Medication		
Varenicline	Reference	Reference
NRT	0.81 (0.63 –1.03)	**0.71 (0.54 –0.94)***
Cessation Rx given by specialty care physician?		
No	Reference	Reference
Yes	0.63 (0.28 –1.40)	0.70 (0.31 –1.59)
Received any medication that might affect smoking status anytime 1 year prior to index date		
No	Reference	Reference
Yes	0.71 (0.42 –1.21)	0.74 (0.43 –1.27)
Smoking counseling received anytime one year prior to index date		
No	Reference	Reference
Yes	0.95 (0.74 –1.20)	0.90 (0.70 –1.16)
*** p≤0.05**		

Sensitivity analysis (1) – applying different follow up periods

When applying the shorter follow up period (from index date up to 12 weeks), the hazard ratio for smoking cessation medication became non significant (HR=1.13, 95% CI= 0.86 – 1.50). The results could be found in the following Table 4.

Table 4. Hazard ratios for cessation medication among the cohort (results of original and sensitivity analysis)

	Medication	Adjusted HRs
Overall cohort (n=580)	Varenicline NRT	Reference **0.71 (0.54 – 0.94)***
Sensitivity analysis: follow up period from index date – 12 weeks (n=675)	Varenicline NRT	Reference 1.13 (0.86 – 1.50)

Sensitivity analysis (2) – sub-sample analysis

Quitting smoking or not is very likely to have an effect on cardiovascular risks as well. If we were to control for abstinence, we would also control for part of the medication, and the effect of the medication would be attenuated. Therefore, sub-population analyses with one group among quitters at year 1, another group among non-quitters at year 1, and one more for those with missing smoking status at year 1 were performed. The hazard ratios of our primary interest variable "medication" for all the sub-sample analyses can be found in Table 5.

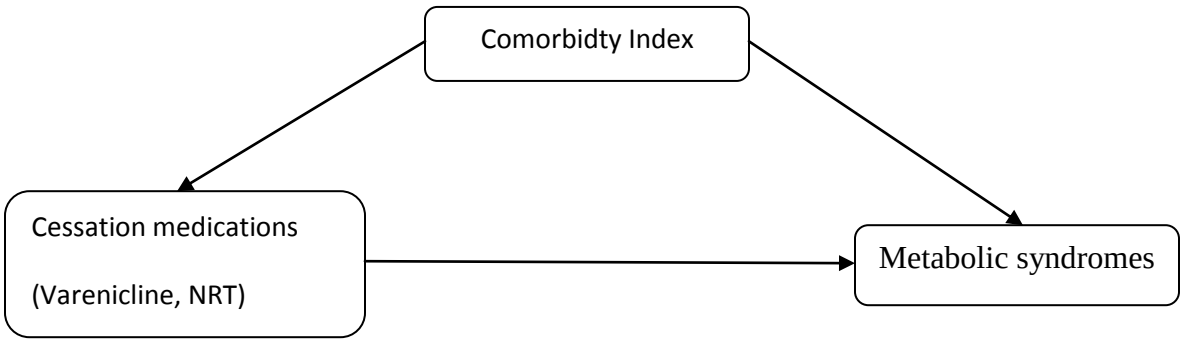
Table 5. Hazard ratios for cessation medication among our cohort and sub-samples

	Medication	Adjusted HRs
Overall cohort (n=580)	Varenicline NRT	Reference **0.71 (0.54 –0.94)***
Quit at year 1 (n=59)	Varenicline NRT	Reference 0.95 (0.40 –2.25)
Did not quit at year 1 (n=234)	Varenicline	Reference

	NRT	0.95 (0.57 –1.59)
Smoking status missing at year 1 (n=287)	Varenicline NRT	Reference **0.47 (0.28 –0.78)***

The overall risk of metabolic syndromes were significantly lower for NRT (HR=0.71, 95% CI=0.54 – 0.94). When the sub-sample analyses among quitters and non-quitters were carried out, risks were no longer statistically significant. For those with missing smoking status at year 1, risks of metabolic syndromes were also significantly lower for NRT (HR=0.47, 95% CI=0.28 – 0.78).

We examined the relationships between "cessation medications + cohort characteristics", "cohort characteristics + metabolic syndromes outcome" and "cessation medications + metabolic syndromes outcome"; we could therefore infer the confounders in our hazard ratio regression model. As we could see from the figure below, comorbidity index was a confounder that affects the cessation medication exposure and our metabolic syndrome outcome.



DISCUSSION

Our study objective was to compare cardiovascular risk factors after using different smoking cessation medications among schizophrenic patients. This is the first study, to our

knowledge, that examined the relationship between cessation medications and several metabolic syndromes among schizophrenic patients. Metabolic syndrome indicators were based on the National Cholesterol Education Program's (NCEP) criteria, which included: (1) elevated fasting glucose (≧110 mg/dl), (2) elevated triglycerides (≧150 mg/dl), and (3) blood pressure level (≧130/ ≧85 mm Hg) [59]. We found nearly half (n=276, 47.59%) of the 580 cohort developed one or more criteria of the metabolic syndromes within just one year after cessation medication exposure. The rate of metabolic syndrome found in our study was extremely high and is in need of addressing. Previous studies had only examined the incidence rates of metabolic symptoms after exposure to antipsychotics. De Hert et al. [103] conducted a study among schizophrenic patients (n=102) in 2006. They found that after the second generation antipsychotics exposure, 27 patients (26.5%) developed metabolic syndromes during an average 3.2 years of follow up. Our study follow up timeline was one year only but the incidence rate was almost double that reported in their study. This indicated that our cohort population is under higher risks and the reasons are described as follows: Substantial concerns were established for SGAs such as changes in body weight, glucose utilization, or lipid status [47]. On top of that, research has demonstrated each cessation medication may have varying effects: NRT has been shown to reduce sensitivity to insulin and may precipitate diabetes [56]. Bupropion has been shown to inhibit enzyme CYP2D6 and would reduce the clearance of drugs metabolized by it (atypical antipsychotics) thus in turn increase the chances of developing metabolic side effects [28]. Manufactures of Varenicline have been required by FDA to conduct a systematic review of all randomized clinical trials to determine its association with cardiovascular risks [58]. With both the side effects of antipsychotics and cessation medications combined, the risk would therefore be higher for our population. We need to pay close attention when these metabolic syndromes

present as such patients have a higher of cardiovascular events sometime in the future. A meta-analysis indicated that individuals with the metabolic syndrome have a 61% increased risk of cardiovascular disease compared to individuals without the metabolic syndrome [104]. Metabolic abnormalities are also associated with a lower functional outcome, a worse perceived physical health, poorer quality of life and non-compliance to the medication [103].

In our analysis, we did not include smokers who were on Bupropion because of sample size limitations. We found smokers who were prescribed NRT were less likely to develop cardiovascular risk factors as compared to those who were prescribed Varenicline (HR=0.71, 95% CI=0.54 – 0.94). This indicates that Varenicline might have some drug interaction effects with the antipsychotics patients were already taking. The mechanism behind Varenicline leading to cardiovascular risk is still unknown but its label was updated accordingly with warnings of elevated cardiovascular events. NRTs are mainly OTCs and are generally considered to be safer. Therefore, healthcare professionals are advised to carefully weigh the risks of Varenicline against the benefits of its use. Patients should also be notified to contact their physicians if they experience any chest pain or shortness of breath symptoms when taking the medication. Patients should also have their blood work done at least once a year or even once every 6 months. With blood test checked regularly, we could ensure their blood glucose levels and cholesterol levels are under control. Life style should be adjusted if they were to find some of the cardiovascular indicators exceed the normal ranges [105].

However, when applying the different follow up period (from index date to 12 weeks), we actually found NRT had 13% higher risks in developing cardiovascular risk factors as compared to Varenicline. This result, however, was not significant with 95% confidence interval 0.86 – 1.50. We also conducted another sensitivity analysis (sub-group analysis) among those

who had quit and those who had not, but a large number of patients had missing smoking status. The hazard ratio for medication was also no longer statistically significant: quitters (HR=0.95, 95% CI=0.40 – 2.25) and non quitters (HR=0.95, 95% CI=0.57 – 1.59). Hazard ratios were very close to 1 with 0.95 for both of the sub-group analyses. There was about a 33% increase for hazard ratio when compared to the overall hazard; indicated sub-sample analyses might not be consistent with the original finding. We then conducted similar analysis among those who did not have smoking status recorded by year 1. Significant lower hazards were found for NRT (HR=0.47, 95% CI=0.28 – 0.78). Therefore, the overall significant hazards were probably driven by patients who did not have smoking status recorded and we were unable to assess the effect of quitting vs. not on the outcome. With the non significant findings of medications (for different follow up periods as well as sub-sample analysis), this indicated the cessation medications might not have different effects toward the development of cardiovascular risk factors. It might be the fact of quitting smoking that played the role in affecting cardiovascular risk factors and future research is needed to investigate the quitting effect.

Several trials have demonstrated a lesser post cessation weight gain when using Bupropion [11, 106]. At the end of treatment, participants taking Bupropion were found to gain significantly less weight than those on placebo [-1.11kg (-1.47 to -076)] [11] with about 3.8 vs. 5.6kg at 1-year and 4.1 vs. 5.4kg at 2-year follow-up [107]. On the other hand, Varenicline did not have significant effects on weight at the end of treatment when compared to placebo [107-109]. This indicated when schizophrenic patients are considering quitting, Bupropion might be a better option for them or for those who have family histories of diabetes, hyperlipidemia or high blood pressure. Future studies should include more patients who tried to quit with Bupropion so

the medication effect on weight could be tested in this minority population. More schizophrenic smokers should also be included to increase statistical power.

We also found higher levels of BMI and comorbidity index were more likely to develop cardiovascular risks. These findings were expected because BMI is reported to be positively associated with hypertension and dyslipidemia, and obesity is associated with diabetes [110]. It is estimated that for every 1-kg increase in weight, the prevalence of diabetes increases by 9% [111]. Similarly, the prevalence of cardiovascular disease among people in the normal weight ($18.5 \leq BMI < 25$), overweight ($25 \leq BMI < 30$), and obese ($BMI \geq 30$) groups is 20%, 28%, and 39%, respectively [112]. In a recent, large, prospective cohort study included 12,550 adults, the development of type 2 diabetes was almost 2.5 times more likely in patients with hypertension than in their counterparts [113]. Moreover, Gress et al found that hypertensive patients who were taking beta-blockers had a 28% higher risk of diabetes than those did not take the medication [114]. This suggests these 3 common chronic diseases frequently coexist.

We also found males were more likely to develop elevated glucose/cholesterol/blood pressure than females (HR=1.47, 95% CI=1.14 – 1.89). Sex differences in cardiovascular risks have been discussed in previous research and the findings varied among studies. North American surveys indicate that cardiovascular diseases are more prevalent in men in the US, with 8.4% of men vs. 5.6% of women; however, the incidence has been declining in men and remained stable in women. Possible reasons for gender association with cardiovascular disease include higher rates of overweight and cigarettes smoking for men; on the other hand, reasons for females include less physically activity and diminishing estrogen levels during premenopausal and menopausal phase. Adolescent girls and premenopausal women tend to have more favorable risk profiles with lower levels in cholesterol and glucose [115]. However, levels plateau in men and

increase in women between ages 40 and 60 years. For example, LDL level increases at an average rate of 0.05mmol/L a year for women. One study using NHANES data examined sex differences on blood pressure. They reported men had higher systolic blood pressure levels than women among US adults less than 45 years of age. By 60–69 years of age, women had blood pressure levels similar to those of men and by 70–79 years of age, had higher levels than men [115]. This increase at menopause is thought to be partly the result of advancing age and declining levels of estrogen [115].

Strengths and Limitations

The limitations in this study are mainly related to using EMR data: (1) we could not track if patients picked up the medication at a pharmacy. Medication data were identified by physician orders, which did not guarantee that the patients actually filled the prescription. (2) We are not certain how compliant the patients were. Unlike chronic medications, cessation products are usually for a short term use, so compliance should not be a significant problem [96]. (3) Some important variables were with missing information, for example, the stop dates of medications were sometimes missing and smoking status was not recorded regularly. The missing values may limit generalizability of our findings. Furthermore, information was not recorded in GE data for some possible confounders like nicotine addiction level (or how many cigarettes they smoke per day), eating habits, physical activities, and family history for some diseases. We tried to infer nicotine addiction level from the NRT dosages they got but we would not be able to do so for those who were on Varenicline because the dose is fixed. Those who got Varenicline were assumed to have a high addiction as they did not go for the choice of easily accessible NRT. We might underestimate the percentage of those on NRT because majority of products are over the

counter. Smokers might not mention that information to their doctors if not being asked; therefore, it would not be recorded in GE EMR.

Despite the limitations described above, the population distribution in GE EMR is very similar with the US population and thus is representativeness of outpatient practice. It is also rich in clinical information including vital signs, laboratory results, medication list entries or prescriptions, and diagnoses or problems. With proper smoking status and smoking cessation medications (including NRT OTCs), it was considered an appropriate database for our research questions. No studies have been conducted with this population examining the associations between cessation medications and cardiovascular risks. Our findings are important to fill the gap in research as warnings were noticed for general populations and were not adequately explored for this minority sub-group who are already under higher risks of developing cardiovascular risk factors.

CONCLUSIONS

Individuals with the metabolic syndrome have high risk of developing cardiovascular diseases in the future. In our study, we found nearly half (n=276, 47.59%) of the 580 cohort developed one or more criteria of the metabolic syndromes within just one year after the cessation medication. Bupropion was not included in this analysis because of low sample size and we found smokers who were prescribed NRT were less likely to develop metabolic syndromes as compared to those who were prescribed Varenicline. However, when applying different follow up periods and sub-sample analysis, there were no differences between the medications. With the non significant findings, this indicated cessation medications might not have different effects toward the development of cardiovascular risk factors. It might be the fact of quitting smoking that played the role in affecting the outcomes. Since the rates of developing

metabolic syndromes are so high, healthcare professionals are advised to carefully weigh the risks of cessation medications against the benefits before use. Other predictors we found that were associated with cardiovascular risks included being male gender, with higher levels of BMI and comorbidity index.

MANUSCRIPT 3

Comparison of Suicide Attempts/Behaviors following Smoking Cessation Treatments among Schizophrenic Smokers

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INTRODUCTION

Smoking is a serious public health problem. Tobacco use causes approximately 443,000 premature deaths annually in the United States (US) [1, 2] and 5.4 million worldwide [3]. As compared to the general population, schizophrenic patients have much higher smoking rates. According to previous studies, 72% - 90% of patients with schizophrenia smoke cigarettes, compared with 23% in the general population [4]. The high prevalence can be possibly due to the self-medication effect of tobacco [22]. Tobacco may be used to alleviate some of the symptoms in schizophrenia and the side-effects of antipsychotic medications [23]. Quitting smoking may worsen their psychiatric symptoms, therefore, these patients cannot and do not want to quit their tobacco use [25]. Previous studies have also shown that schizophrenic patients tend to be heavy smokers [5], to have much lower smoking cessation rates and higher nicotine dependence level [6, 7]. Although individuals with schizophrenia constitute approximately only less than 1% of the general population as mentioned earlier, the medical and economic burden of cigarette smoking among mentally ill patients is enormous [6]. Thus, there is great public health significance in developing safe and effective tobacco cessation pharmacotherapies in this population.

Smoking cessation is highly recommended by public health department of various organizations and several smoking intervention strategies are available for smokers. During the 1990s, a variety of pharmaceutical cessation aids became available, which include nicotine replacement therapy (NRT) and the antidepressant Bupropion SR [8]. Even more recent, Varenicline was approved as an aid to smoking cessation [9]. The FDA suggested dosage regimen for cessation pharmacotherapy is usually for 12 weeks.

Suicide is the leading cause of premature death among patients with schizophrenia. Overall, patients with schizophrenia have approximately a 50% lifetime risk for suicide attempts and a 9-13% lifetime risk for completed suicide. In comparison, the lifetime risk for suicide in the general population of the United States is approximately 1% [13]. Most of the completed suicides appear to occur within the first 10 years after illness onset and 50% occur within the first 2 years; however, the risk of suicidal behaviors is lifelong [67].

Many of the important risk factors for suicide in schizophrenia were similar to those in the general population, including being young, male, and with a high level of education, mood disorder, previous suicide attempts, and drug misuse [68, 69]. There are, however, other risk factors that are specific to the disorder. A systematic review with 29 eligible studies identified some of predictors: previous depressive disorders (OR=3.03, 95% CI: 2.06 - 4.46), previous suicide attempts (OR=4.09, 95% CI= 2.79 - 6.01), drug misuse (OR=3.21, 95% CI= 1.99 - 5.17), agitation or motor restlessness (OR=2.61, 95% CI=1.54 - 4.41), fear of mental disintegration (OR=12.1, 95% CI=1.89 - 81.3), poor adherence to treatment (OR=3.75, 95% CI= 2.20 - 6.37) and recent loss (OR=4.03, 95% CI= 1.37 - 11.8). Reduced risk was associated with hallucinations (OR=0.50, 95% CI= 0.35 - 0.71) [68] and adherence to antipsychotic treatments [69].

Quitting smoking may (1) lead to major depression in some smokers and (2) result in a withdrawal syndrome that includes worsened mood and other behaviors that would increase the risk of suicide. Many studies have found that negative affect symptoms are the most common symptoms of tobacco withdrawal. The U.S. Food and Drug Administration (FDA) have required black box warnings for patients regarding serious psychiatric side effects for two pharmacological treatments, Varenicline and Bupropion. The warnings refer to suicidal/self-

injurious behaviors and also depression [14]. Some epidemiological studies reported the increased risk for suicidal/self-injurious behaviors and depression are due to smoking cessation medications and are independent of quitting [14]. Since our cohort is schizophrenic patients, co-existing of anxiety and depressions are common clinical symptoms in most patiens, and our objective is to investigate suicidal/self-injurious behaviors among patients attempting to quit smoking.

To date, no studies have been conducted among this specific minority population examining which cessation medication could lead to lower risks of suicide attempts or behaviors. This information is critical for healthcare professionals as they may need to monitor their patients more closely during the process of quitting.

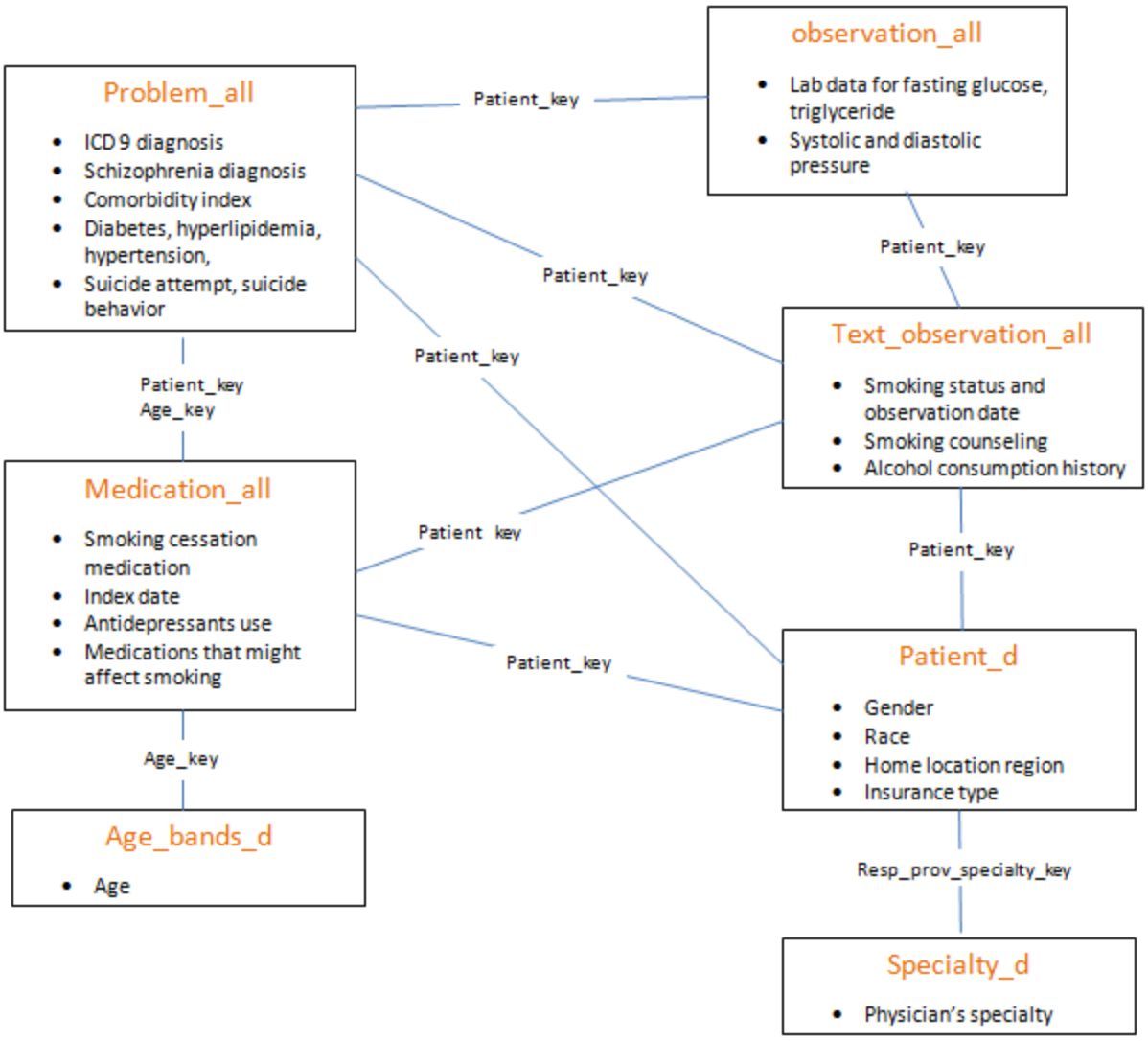
METHODS

Data source

The data used for this study were extracted from the General Electric Centricity Electronic Medical Record (GE EMR) research database. The Centricity EMR database is used by more than 20,000 clinicians and contains longitudinal ambulatory electronic health data for more than 7.4 million patients, including demographic data, vital signs, laboratory orders and results, medication list entries and prescriptions, and diagnoses or problems. A variety of practice types are represented in the database, ranging from solo primary care practitioners to community clinics, academic medical centers, and large integrated delivery networks [73]. Both medications and prescriptions are documented in the database. Medications may include a broader list of all medications that a patient is taking including over the counter medications, herbal remedies and medications prescribed by a provider that may be out of the EMR network. On the other hand, prescriptions are medications that have been prescribed by the responsible provider of this

patient within the EMR. The availability of smoking status as well as information regarding OTC medications use like NRT, which cannot be captured in most of the claims data, makes the GE EMR dataset an appropriate clinical database for this research. Data are collected centrally and go through a quality-control process to remove invalid values [74]. One study using 2005 data found the population distribution is very similar between GE EMR and the US population. The proportion of patients aged 18 to 64 years in the GE EMR population was 63%, which is similar to that in the US general population. Furthermore, of the patients in the GE EMR whose race is documented, 79% were white and 15% black, compared with 81% white and 13% black in the US population [74]. GE data set has been widely used in studying smoking, for example, Fox et al. assessed effectiveness of different statins among diabetes mellitus patients with smoking status as one of the covariates [75]. GE data consists of several different files that give different information, for example, "problem file" has information with ICD9 diagnosis, "text observation file" has information with smoking status, or "patient_d_file" has patients' demographics information. The protocol to linking the different files together is detailed in Figure 1 below.

Figure 1: Linkage between GE data files



Study population

From the GE healthcare EMR databases, we identified patients with a diagnosis of schizophrenia or schizoaffective disorder (ICD-9 code 295.00-295.99) [76].

After identifying the population, we constructed a series of new-user cohort of patients who had newly initiated use of smoking cessation medications. Only the first exposure to each of the smoking cessation medication was examined so we can be sure that quitting is not affected by the previous cessation product they took. Those who were prescribed more than one medication the same day as their index medication were excluded. The first day of being

prescribed smoking cessation medication was defined as the index date. We included patients who aged 18 years or older and who were enrolled between 12/13/1995 to 10/31/2011. In order to make sure Wellbutrin® (Bupropion SR) would not affect patient's smoking status, we excluded those who were prescribed antidepressant Wellbutrin® (Bupropion SR) 6 months prior to index from this study.

Definitions of suicidal/self injurious behaviors

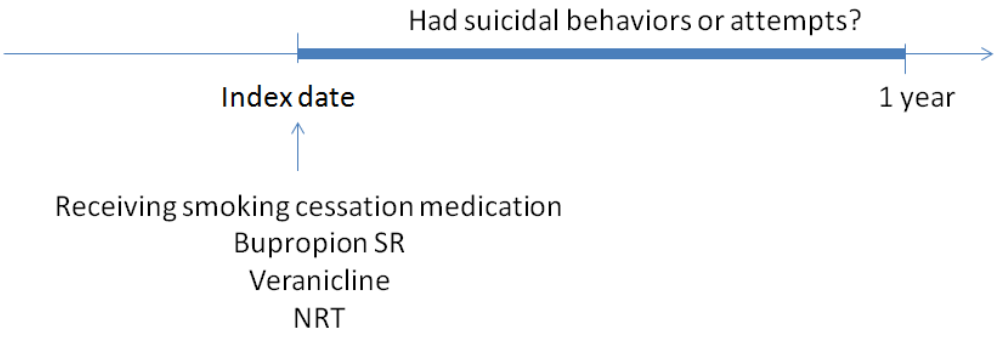
We recognized patients' suicidal behaviors or attempts through ICD9 codes in the problem file. From the literature search, we identified a wide range of ICD9 codes and E-codes that have been used before with the similar suicidal outcomes, for example, poisoning by solid or liquid (E950); hanging, strangulation, or suffocation (E953); drowning (E954), or jumping from a high place (E957) [116, 117].

Analysis Plan

In order to examine if there are any differences in cessation medication prescription type with patient characteristics, we first carried out descriptive statistics and chi-square analyses. We then used the Cox proportional hazards model to study the factors associated with suicidal/self injurious behaviors developed over the course of follow-up. Observation began on the day (index day) a patient received his or her first exposure of smoking cessation medication (NRT, Bupropion, or Varenicline) and continued until one year after the treatment exposure. Patients would either had the behavior or be censored at the end of follow up. They were censored if they satisfied any of the three conditions below: (1) the last day the index medication being prescribed, (2) switching over to (or adding on) another smoking cessation medication, and (3) did not have records for suicide attempts or behaviors when they reached the one year follow up. The total

duration (t=months) was calculated as the date of the endpoint (the date patient had the behavior or being censored) minus index date divided by 30. Please see Figure 2 for the analysis plan.

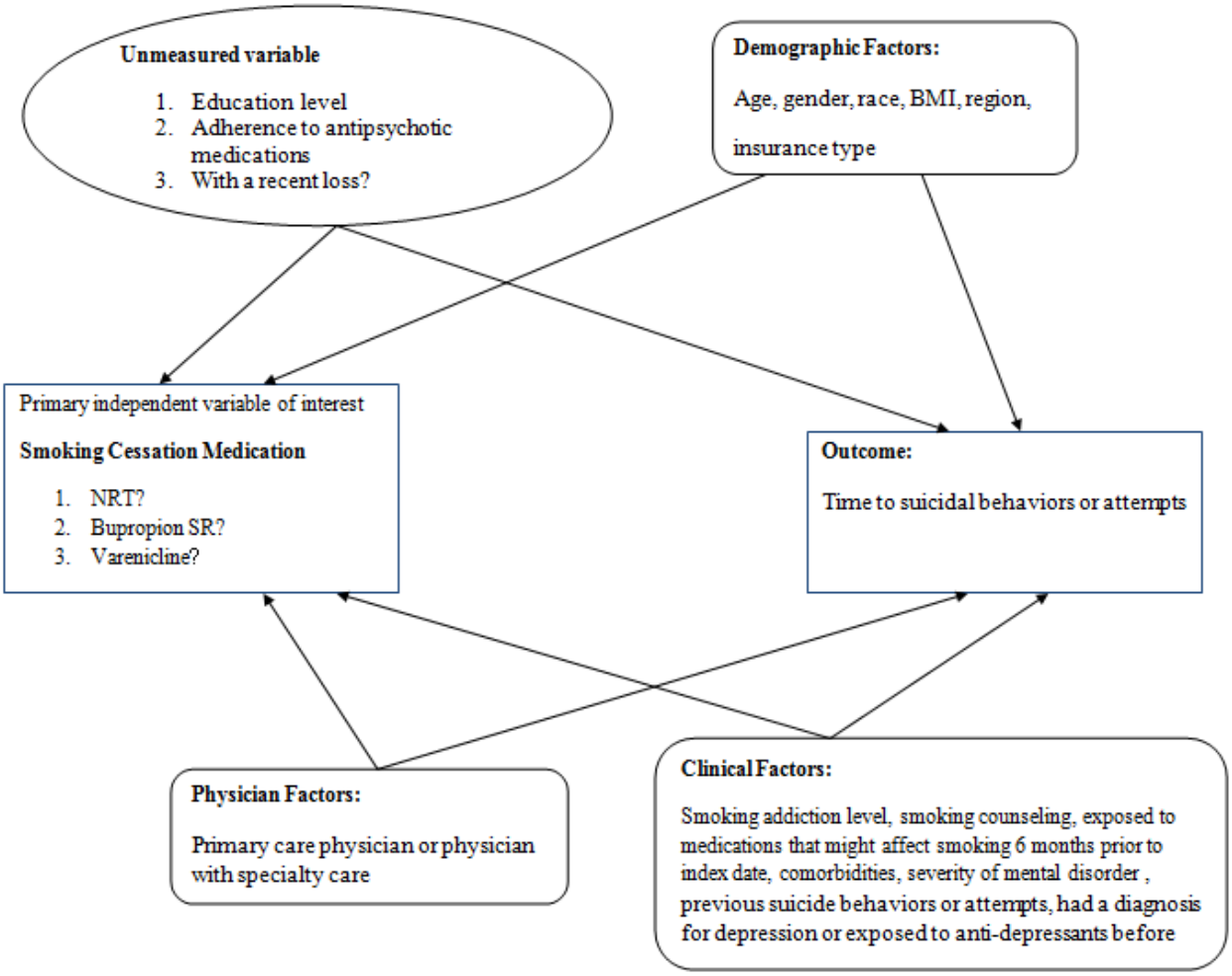
Figure 2: Analysis plan



The primary outcome of interest in this Cox regression model was the cessation medication they received (NRT, Bupropion SR or Varenicline). Other potential confounders were included in Cox regression model as well, which included: age, race, gender, region (Midwest, Northeast, South, West), BMI (normal, over-weight, or obese), payment type (government or non-government insurance), specialty group (primary care, specialty care), had previous suicide behaviors/attempts or depression/exposed to anti-depressants one year before index date (yes/no) [69] [118], nicotine addiction level, comorbidity index, and severity of mental disorder (having antipsychotic injections anytime one year before index date). We tried to infer nicotine addiction level from the NRT dosages they got. If their starting dose for nicotine patch was 21mg/day or nicotine gum 4mg/piece then they were classified as high nicotine addiction; on the other hand, if their starting dose for nicotine patch was 14mg/day or 7mg/day, or nicotine gum 2mg/piece, then they were classified as low nicotine addiction. However, we would not be able to do so for those who were on Varenicline because the dose is fixed. Those who got Varenicline were assumed to have a high addiction as they did not go for the choice of

easily accessible NRT. Education level, adherence to their anti-psychotic medications and whether they had a recent loss were not recorded in GE data so those could be unmeasured counfounding factors. Figure 3 below shows the conceptual model for time to suicidal behaviors or attempts.

Figure 3. Conceptual model for time to suicidal behaviors or attempts



There are some assumptions that we have to satisfy for conducting the survival analysis. The proportional hazard assumption was checked for all the independent variables one at a time in the model by using Schoenfeld test. If our primary independent variable (cessation medication) were to violate the assumption, time dependent variable would then be created using heavyside

function to adjust for time in the analysis. On the other hand, for other independent variables that were to violate the assumption, we would carry out further analyses with those variables being stratified. We first did a univariate Cox regression analysis for each of the independent variable and included variables with $p<0.2$ or important possible confounders in the multivariate Cox regression model. Demographic variables like age, gender or race, were included in the multivariate model regardless of the significance levels in the univariate analysis. Interaction terms between the main predictor and other independent variables were tested as well. Hazard ratios (HRs) and its 95% CI were used to present the results for the final Cox regression model.

Sensitivity analysis (1) – applying different follow up periods

A shorter follow up period was performed: from index date up to 12 weeks. This was to examine if the results remained robust when applying different timelines.

Sensitivity analysis (2) – sub-sample analysis

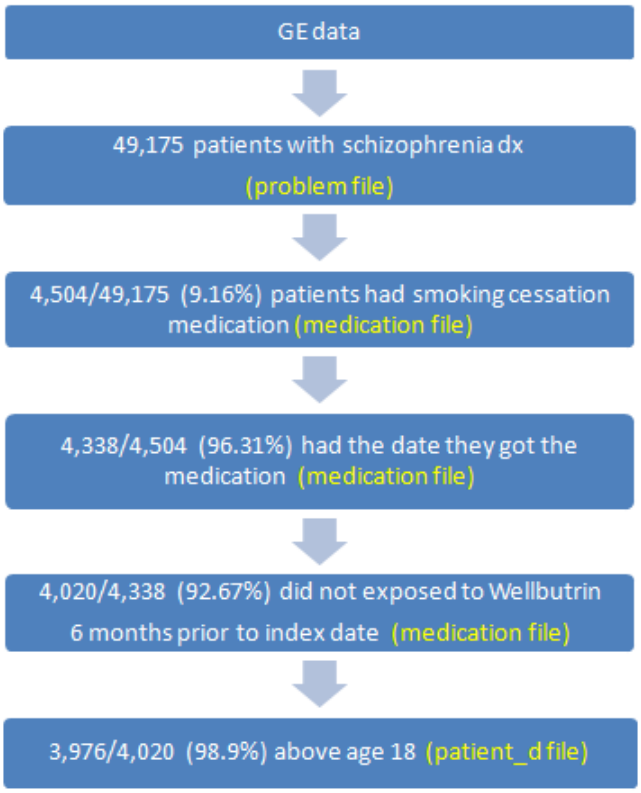
The previous analysis was conducted among all the patients who meet the inclusion criteria. We believed that quitting smoking would have a significant effect on suicide because of negative emotions. However, as shown in the previous survival model, quitting smoking or not was not one of the independent variables, but the cessation medication was. Abstinence is the effect of cessation medication so if we are to control that, we are like controlling for part of the medication's effect, the effect of medication will therefore be attenuated. To avoid that, we did two stratified analyses: one for those who quit at year 1 and the other one for those who did not.

RESULTS

Cohort distribution

From the inception of GE data, we found there are a total of 49,175 patients had at least one diagnosis of schizophrenia or schizoaffective disorder (from December 1995 to October 2011). About 10% of them received at least one cessation medication prescription at any point (n=4,504, 9.16%). Most of the dates they received the medication were recorded (n=4338, 96.31%) and those without the dates were dropped. To meet our study exclusion criteria "individual aged below 18 years old" or "those who received antidepressants Bupropion (Wellbutrin®) at any point 6 months prior to index date" were also excluded from our study cohort. This brought the sample size down to a total of 3,976 patients. Please see Figure 4 below for how we identified our population.

Figure 4. Identification of our population



After applying the exclusion criteria "being prescribed more than one medication the same day as their index medications", the cohort came down from 3,976 to 3,925.

Please see Table 1 and Table 2 for patients' characteristics by different cessation medications and by outcome. Slightly more than half were of male gender (n=2,115, 53.89%), almost half were whites (n=1,786, 45.50%), and majority were with high nicotine addiction level (n=3,166, 80.66%). Almost all of them had stable mental state as only 2.34% (n=92) of the cohort had been prescribed antipsychotics in the injection form at any point 1 year prior to index date. Slightly more than half (n=2,016, 53.57%) of the cessation medication users were under Medicare or Medicaid coverage. The mean age of the cohort was 45.40 years old (± SD: 11.49) with a minimum of 18 and a maximum of age 80. Most of the cessation medications were prescribed by their primary care physicians (n=3,809, 97.04%) and about forty percent of the patients had received smoking counseling from their healthcare providers anytime one year prior

to index date (n=1,589, 40.48%). As it shows in Table 1, NRT (n=2,627, 66.93%) was prescribed more commonly compared to Varenicline (n=1,207, 30.75%) and Bupropion (n=91, 2.32%).

From the previous literature, the best way to predict suicide is past suicide experiences. Only 1 patient out of the 3,925 cohort had suicide behavior during one year prior to index date, and even from the inception of data, there have been only 6 suicide behaviors recorded in patients' diagnosis file. The sample size was too small to be coded as one of the independent variables in the model; therefore, we combined that together with depression (yes vs. no). About sixty percent of patients had depression diagnosis or were on at least one anti-depressant at some point (n=2373, 60.46%) during one year prior to index date.

Among the 3,925 cohort, there were 104 of them had suicide attempts or behavior just within one year after the cessation exposure. The number of suicide increased dramatically after the exposure within such a short time frame.

Predictors for suicidal attempts or behaviors during 1-year follow up time period

Most of the independent variables in the model met Schoenfield assumption except for race and BMI. Though violating the assumption, it seemed fine from the survival distribution plots, as the lines were close to parallel and no cross overs were detected (between each group). However, to make sure we have a precise model, we conducted further survival analyses with race and BMI being stratified. In that case, we could no longer understand how those links to the outcome, which is ok, because they are not our primary interest variables in this objective. Sensitivity analysis was conducted with race and BMI included in the multivariate PH regression model and the coefficient estimates remained similar indicated our model was robust.

No interactions were found between the cessation medications and other independent variables using chunck test. The model with all the interaction terms was not statistically different from the model without the interactions: likelihood ratio difference between the two models (all independent variables and all independent variables + interactions) was 11.702, giving a non significant $p > 0.2$ at 12 degrees of freedom.

As we can see the hazard ratios from Table 3, only comorbidity index was found to be associated with time to suicide among all the independent variables we included in the model. It showed that the higher the Charlson comorbidity indices, the higher risks of suicide behaviors or attempts within one year (HR=1.15, 95% CI=1.04 – 1.27).

Table 1. Overall baseline characteristics of the study cohort and numbers (percentages) within each cessation medication

Characteristics	Overall cohort Total Frequency (Percentage)	Varenicline N=1207 (30.75)	NRT N=2627 (66.93)	Bupropion N=91 (2.32)	p-values
Demographics					
Sex					
Female	1810 (46.11)	560 (46.40)	560 (46.40)	51 (56.04)	0.1433
Male	2115 (53.89)	647 (53.60)	647 (53.60)	40 (43.96)	
Age (years)					0.6828
Race					
Blacks	615 (15.67)	125 (10.36)	476 (18.12)	14 (15.38)	**<0.0001***
Whites	1786 (45.50)	586 (48.55)	1166 (44.39)	34 (37.36)	
All others	1524 (38.83)	496 (41.09)	985 (37.50)	43 (47.25)	
Region					
Midwest	1073 (27.36)	276 (22.89)	785 (29.90)	12 (13.19)	
Northeast	1266 (32.28)	294 (24.38)	947 (36.08)	25 (27.47)	**<0.0001***
South	915 (23.33)	358 (29.68)	519 (19.77)	38 (41.76)	
West	668 (17.03)	278 (23.05)	374 (14.25)	16 (17.58)	
BMI					
Normal (BMI<25)	1460 (37.20)	443 (36.70)	976 (37.15)	41 (45.05)	
Overweight (25<=BMI<30)	864 (22.01)	259 (21.46)	587 (22.34)	18 (19.78)	0.5277
Obesity (BMI>=30)	1601 (40.79)	505 (41.84)	1064 (40.50)	32 (35.16)	
Insurance					
Not Medicare/Medicaid	1747 (46.43)	511 (44.28)	1189 (47.13)	47 (54.65)	0.0832
Medicare or Medicaid	2016 (53.57)	643 (55.72)	1334 (52.87)	39 (45.35)	
Clinical factors					
Comorbidty Index					**0.0008***
Had antipsychotic injectables 1 year prior to index date					
No	3833 (97.66)	1181 (97.85)	2562 (97.53)	90 (98.90)	0.6061
Yes	92 (2.34)	26 (2.15)	65 (2.47)	1 (1.10)	
Smoking Cessation Related					

Addicted to nicotine					
No	759 (19.34)	0 (0.0)	759 (28.89)	0 (0.0)	**<0.0001***
Yes	3166 (80.66)	1207 (100.0)	1868 (71.11)	91 (100.0)	
Cessation Rx given by specialty care physician?					
No	3809 (97.04)	1161 (96.19)	2558 (97.37)	90 (98.90)	0.0756
Yes	116 (2.96)	46 (3.81)	69 (2.63)	1 (1.10)	
Received any medication that might affect smoking status anytime 1 year prior to index date					
No	3749 (95.52)	1167 (96.69)	2497 (95.05)	85 (93.41)	**0.0467**
Yes	176 (4.48)	40 (3.31)	130 (4.95)	6 (6.59)	
Smoking counseling received anytime one year prior to index date					
No	2336 (59.52)	748 (61.97)	1525 (58.05)	63 (69.23)	**0.0115**
Yes	1589 (40.48)	459 (38.03)	1102 (41.95)	28 (30.77)	
Had depression or suicide experiences before					
No	1552 (39.54)	409 (33.89)	1094 (41.64)	49 (53.85)	**<0.0001***
Yes	2373 (60.46)	798 (66.11)	1533 (58.36)	42 (46.15)	
Total cohort=3925; * p≤0.05					

Table 2. Suicidal attempts/behaviors by patient charateristics during 1-year follow up

Characteristics	Suicidal attempts/behaviors (n=104, 2.65%)	
	Number (%)	Hazard ratio p-values
Demographics		
Sex		
Female	52 (2.87%)	0.3674
Male	52 (2.46%)	
Age (years)		0.4001
Race		
Blacks	11 (1.79%)	**0.0279***
Whites	60 (3.36%)	
All others	33 (2.17%)	
Region		
Midwest	23 (2.14%)	
Northeast	33 (2.61%)	0.2277
South	24 (2.62%)	
West	24 (3.59%)	
BMI		
Normal (BMI<25)	43 (2.95%)	0.4863
Overweight (25<=BMI<30)	18 (2.08%)	
Obesity (BMI>=30)	43 (2.69%)	
Insurance		
Not Medicare/Medicaid	51 (2.92%)	0.2615
Medicare or Medicaid	46 (2.28%)	
Clinical factors		
Comorbidty Index		**0.007***
Had antipsychotic injectables 1 year prior to index date		
No	103 (2.69%)	0.4025
Yes	1 (1.09%)	
Smoking Cessation Related		

Addicted to nicotine No Yes	 19 (2.50%) 85 (2.68%)	0.7348
Cessation Medication Varenicline NRT Bupropion	 65 (2.47%) 37 (3.07%) 2 (2.20%)	0.3617
Cessation Rx given by specialty care physician? No Yes	 101 (2.65%) 3 (2.59%)	0.9722
Received any medication that might affect smoking status anytime 1 year prior to index date No Yes	 100 (2.67%) 4 (2.27%)	0.6563
Smoking counseling received anytime one year prior to index date No Yes	 56 (2.40%) 48 (3.02%)	0.2542
Had depression or suicide experiences before No Yes	 37 (2.38%) 67 (2.82%)	0.3658
Total cohort=3,925; * p≤0.05		

Table 3. Predictors for Suicidal attempts/behaviors during 1-year follow up

Characteristics	Suicidal attempts/behaviors (n=104, 2.65%)	
	Unadjusted HRs	Adjusted HRs
Demographics		
Sex		
Female	Reference	Reference
Male	0.84 (0.58 –1.24)	0.89 (0.59 –1.34)
Age (years)	0.99 (0.98 –1.01)	0.99 (0.97 – 1.01)
Race		
Blacks	Not meeting Schoenfield test	
Whites	Being stratified	
All others		
Region		
Midwest	Reference	Reference
Northeast	1.26 (0.74 –2.14)	1.06 (0.60 –1.85)
South	1.28 (0.72 –2.26)	1.11 (0.60 –2.07)
West	**1.82 (1.03 –3.23)***	1.39 (0.75 –2.58)
BMI		
Normal (BMI<25)	Not meeting Schoenfield test	
Overweight (25<=BMI<30)	Being stratified	
Obesity (BMI>=30)		
Insurance		
Not Medicare/Medicaid	Reference	Reference
Medicare or Medicaid	0.80 (0.54 –1.19)	0.83 (0.55 –1.24)
Clinical factors		
Comorbidty Index	**1.14 (1.04 – 1.25)***	**1.15 (1.04 – 1.27)***
Had antipsychotic injectables 1 year prior to index date		
No	Reference	Reference
Yes	0.44 (0.06 –3.09)	0.49 (0.07 –3.52)
Smoking Cessation Related		
Addicted to nicotine		
No	Reference	Reference

Yes	1.09 (0.67 –1.80)	0.97 (0.56 –1.68)
Cessation Medication		
Varenicline	Reference	Reference
NRT	0.76 (0.51 –1.13)	0.81 (0.51 –1.28)
Bupropion	0.66 (0.16 –2.72)	0.37 (0.05 –2.70)
Cessation Rx given by specialty care physician?		
No	Reference	Reference
Yes	1.03 (0.33 –3.22)	0.75 (0.19 –3.04)
Received any medication that might affect smoking status anytime 1 year prior to index date		
No	Reference	Reference
Yes	0.80 (0.30 –2.17)	0.79 (0.29 –2.15)
Smoking counseling received anytime one year prior to index date		
No	Reference	Reference
Yes	1.26 (0.86 –1.84)	1.16 (0.77 –1.74)
Had depression or suicide experiences before		
No	Reference	Reference
Yes	1.21 (0.81–1.80)	1.13 (0.74–1.74)
*** p≤0.05**		

Sensitivity analysis (1) – applying different follow up periods

When applying shorter follow up period (from index date to 12 weeks), we had only a few patients who were prescribed Bupropion and attempted or committed suicide during this time, therefore, we had to exclude those who were prescribed Bupropion for the proportional hazard regression analysis. The hazard ratio for smoking cessation medication remained not significant: HR=0.91, 95% CI= 0.41 – 2.02. Results could be found in the following Table 4.

Table 4. Hazard ratios for cessation medication among our cohort (results for original and sensitivity analysis)

	Medication	Adjusted HRs
Overall cohort (n=3,925)	Varenicline	Reference
	NRT	0.81 (0.51 –1.28)
	Bupropion	0.37 (0.05 –2.70)
Sensitivity analysis: follow up period from index date – 12 weeks (n=3,916)	Varenicline	Reference
	NRT	0.91 (0.41 –2.02)

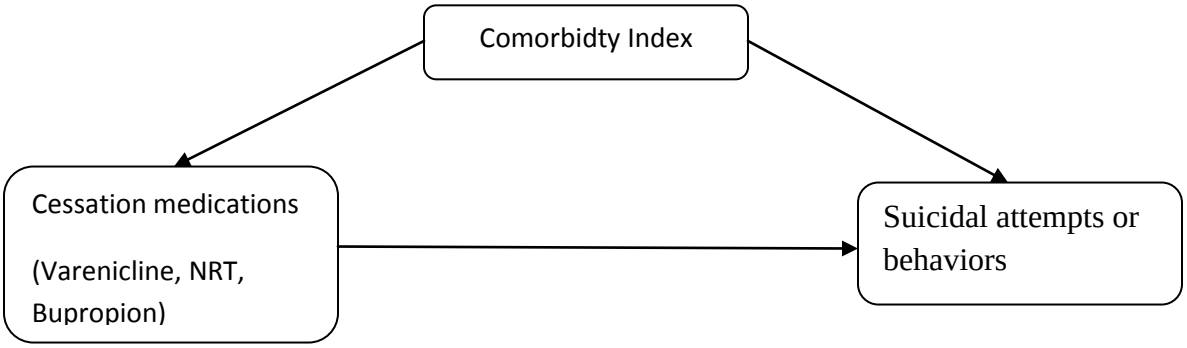
Sensitivity analysis (2) – sub-sample analysis

Quitting smoking or not is also likely to have an effect on suicide. If we were to control for abstinence, we would control also for part of the medication, and the effect of the medication would be attenuated. Therefore, sub-sample analysis with one group among quitters at year 1 and the other group among non-quitters at year 1 were performed. Since only 5 people quit smoking for those who were prescribed Bupropion, we could not do further analysis with the low sample size. Results can be found in Table 5 below. Aside from that, the results seem very consistent throughout three groups with NRT having lower chances in developing suicide as compared to Varenicline. The results were, however, not statistically significant.

Table 5. Hazard ratios for cessation medication among our cohort and sub-samples

	Medication	Adjusted HRs
Overall cohort (n=3,925)	Varenicline NRT Bupropion	Reference 0.81 (0.51 –1.28) 0.37 (0.05 –2.70)
Quit at year 1 (n=334)	Varenicline NRT Bupropion	Reference 0.63 (0.14 –2.84) n/a
Did not quit at year 1 (n=1,649)	Varenicline NRT Bupropion	Reference 0.88 (0.44 –1.77) 1.09 (0.14 –8.63)

We examined the relationships between "cessation medications + cohort characteristics", "cohort characteristics + suicidal outcomes" and "cessation medications + suicidal outcomes"; we could therefore infer the confounders in our hazard ratio regression model. As we could see from the figure below, comorbidity index was a confounder that affects the cessation medication exposure and our suicidal outcomes.



DISCUSSION

Our study objective was to compare different smoking cessation medications (NRT, Bupropion, Varenicline) in leading to lower chances of suicide attempts/behaviors among

schizophrenic patients. We found 104 of our patients (2.65%) had suicide attempts/behaviors within just a year after the medication exposure.

The majority of the 3,925 cohort who were prescribed cessation medications (n=3,833, 97.66%) had stable mental states as they did not have any antipsychotics in injection forms one year prior to index date. This indicates that healthcare system may have been reluctant to prescribe cessation products to those without stable mental states. A potential reason could be the possible beneficial effect of tobacco, which could be used to alleviate some of the symptoms in schizophrenia and reduce the side-effects of antipsychotic medications [23]. Another reason might be that in comparison to the unpredictable positive and negative schizophrenic symptoms, smoking seems to be a small problem and not the primary focus of healthcare providers.

Among the cohort were prescribed cessation medications, almost half were whites (n=1,786, 45.50%), followed by other races (Asians, Hispanics, Multi-races, and Indian Americans) (n=1,524, 38.83%), and blacks (n=615, 15.67%). Previous studies have reported racial inequalities in prescribing among those who were prescribed cessation medications. The causes of these disparities are multi-factorial and complex. Barriers to receipt of treatment could be due to lack of health-insurance coverage or geographic location. However, some previous trials targeted to minority smokers like blacks have demonstrated the efficacy of a variety of smoking cessation treatments provided to them [79]. Therefore, physicians should provide all available cessation strategies to smokers regardless of their races.

Medicaid enrollees are reported to have nearly twice the smoking rates of the general adult population [81]. Schizophrenic smokers are usually with lower social-economic statuses thus more likely to be covered under Medicaid. In our study, we found slightly more than half of

the cessation medications were prescribed to smokers who were under Medicare or Medicaid coverage (n=2,016, 53.57%).

Of the 3,925 patients who were prescribed cessation medications, only 40% of them received smoking cessation counseling during the one year prior to index date (n=1,589, 40.48%). Health professionals are at the forefront of tobacco epidemics as they consult millions of people and can encourage them to quit smoking. In developed countries, more than 80% of the population see a primary care physician at least once a year, and doctors are perceived to be influential sources of information for smoking cessation [83]. Patients see physicians as valuable and credible sources of health information, and patients generally adhere to physician advice [84]. Our results, similarly, showed that the cessation medications were mostly prescribed by their primary care doctors as well (n=3,809, 97.04%). Primary care physicians should take this chance to broaden the reach of effective smoking-cessation counseling.

Among all the medications, NRT was the most commonly prescribed (n=2,627, 66.93%). This could be because NRT products are mostly OTCs and easily accessible at pharmacies or grocery stores. The approval of Bupropion SR (Zyban®) was after NRT, but it was not that commonly prescribed by physicians in this patient population. Prescription rate for Bupropion (Zyban®) (n=91, 2.32%) was even lower than the most recent approved Varenicline (n=1,207, 30.75%). In our cohort of schizophrenic patients, hallucinations and depression symptoms are common comorbid conditions. One would expect physicians to prescribe Bupropion more frequently as it could be used for treating depression and reducing smoking cravings at the same time. Among smokers with a history of depression, there is a twofold higher risk of experiencing recurrent depressive episodes in the one year following cessation from smoking [85]. Even among those who did not originally have negative emotions, a large proportion demonstrated a

depressed mood after quitting [85]. The low prescription percentage we observed here could be due to insurance coverage issues. Insurance companies are more likely to cover depression medications compared to cessation medications, therefore, Zyban® is less likely to be covered under their policies but the same ingredients product Wellbutrin® is usually covered. For instance, the Community Health Plan of Washington (CHPW) did not cover bupropion SR for smoking cessation in 1999, but the plan did cover Bupropion (Wellbutrin®) for mental health indications [86]. When physicians want to prescribe Bupropion to their patients, they might rather prescribe Wellbutrin® but not Zyban® for lower out of pockets expenses for patients. Thus the low rate of Buproprion use (n=91, 2.32%) could be under estimated.

Literature examining suicidal behaviors among schizophrenic patients after cessation medication treatment has been lacking. Suicide is a serious concern among schizophrenic patients because it is the leading cause of death among this minority with rates eight times higher than that in the general population. Our outcome not only included suicide behaviors but also suicide ideations. Suicide attempts are common among schizophrenic patients (about 20-40%) and they often result in death from suicide at a later time [119]. Compared with suicide attempts to the general population, attempts among those with schizophrenia are serious, strong, and lethal [119]. Our results indicate that the number of suicidal attempts or behaviors increased dramatically after the cessation exposure. From the problem file, we only found one patient from our cohort to have committed suicide 1 year prior to index date. Even from the inception of data, we found only 6 patients among the 3,925 of them having suicide records, but after the exposure, the number went up to 104 (2.65% of the cohort) within just a year after the medication. The suicide rate documented here is similar to that of reported in the review. Inskip et al. [120] performed a meta-analysis and the lifetime risk of suicide found was 4% for schizophrenic

patients. Our 2.65% here, however, was observed only one year after the cessation medication exposure. This rate was relatively high and it could be due to the effect of quitting smoking or the cessation medication treatment itself.

Schizophrenic patients who have suicide ideations often contact healthcare workers in the days or weeks before their act [119]. What makes the attempt into the final suicide decision is when the individual thinks he/she is not loved anymore. Pessimistic attitudes evoke and patient stops sharing their emotions with other people. Once these feelings reach a point patient can no longer tolerate, he/she thinks committing suicide is the only solution [121]. Therefore, healthcare providers should pay close attention for all the possible signs of suicide among schizophrenic patients, especially those who are on cessation medications trying to quit smoking.

With regards to comparing the safety within cessation treatments, we found there were no differences between medications and suicide attempts or behaviors. With Varenicline being the reference group, hazard ratios were 0.81 (95% CI=0.51 – 1.28) for NRT and 0.37 (95% CI=0.05 – 2.70) for Bupropion. There were also no statistically significant differences when we applied a shorter follow up period as well as the sub-sample analyses among quitters and non-quitters separately. Reports of suicide have been received for Varenicline and Bupropion and labels for those two medications have even updated with suicide warnings according to FDA's request [14]. Though we did not find any differences in medications, patients still need to be closely monitored when taking these two medications especially that this minority population already has preexisting psychiatric illnesses and suicide is already its leading cause of premature death [13].

Approximately 80% of suicide attempters in the US have a temporally prior mental disorder. Anxiety, depression, mood, impulse-control, and substance disorders all significantly

predict subsequent suicide attempts [122]. From a previous study [123], a quarter of Australian male suicides and a third of female suicides had at least one mention of comorbidity on their death certificates; 12% of the males and 17% of the females had two or more mentions. Among all the total comorbid mentions, psychopathologic conditions were more prevalent than physical diseases. Physical disease comorbidities were mainly documented among elderly suicides and psychopathologic comorbidities predominately among younger populations [123]. In our study, we included previous suicide experiences and depression (both diagnosis and antidepressants) and severity of mental disorders (with having antipsychotics in injection forms as a proxy measure) in the Cox PH regression model but the results did not show any associations with suicide.

As depression is one of the comprehensive negative symptoms in schizophrenia, most patients included in this cohort might have experienced some episodes of depressed mood from time to time which may partially explain the lack of significance with depression. Even though depression is frequently present, it is also often ignored and under-treated [119]. Antidepressants can be used effectively for treating depression without increasing psychotic symptoms, but they are still under-utilized in this at risk population, leading to increased risk for suicidal behavior [119]. Therefore, when depression is identified, it should be treated with pharmacotherapies and psychosocial interventions. We didn't find any associations between depression and suicide but it is considered to be a major risk factor for suicidal behavior across populations.

The only predictor in the multivariate model was comorbidity. As one unit increase in comorbidity index, risk of suicide increased by 15% (HR=1.15, 95% CI=1.04 – 1.27). We used Charlson comorbidity index to measure patients' comorbidities, which includes liver, digestive, chronic pulmonary, and renal diseases, as well as any tumors [124]. Diseases listed above are

mainly chronic and may cause a lot of pain and suffering to patients in addition to the mental disorders. With the deteriorating health condition, quality of life becomes lower and they may reach a point and think it's not worthy of living anymore [125].

We did not find age, sex, race or previous suicide experiences to be associated with suicide, which contradicted with previous evidences. Literature reports that schizophrenic patients who are more likely to commit suicide are young, male, and white, with histories of suicide attempts [119]. The suicide risk for adolescents or young adults with schizophrenia is three times higher than that for adult schizophrenic population. Schizophrenia often starts in early adult life [17] and the first two years of the disease are especially dangerous. Substance misuse like alcohol or opioid dependence could be another reason for younger patients to be under higher suicide risks [119]. Though we intended to include alcohol use into the model but the sample size of alcohol consumption was very low. Physicians didn't seem to record patients' alcohol use into EMR on a regular basis. Tobacco use is a form of substance abuse and our cohort would be all abusers. These uncontrolled potential confounders can partially explain why we did not find age as a significant predictor in this suicide model.

Strengths and Limitations

The limitations in this study are mainly related to using EMR data: (1) we could not track if patients picked up the medication at a pharmacy. Medication data were identified by physician orders, which did not guarantee that the patients actually filled the prescription. (2) We are not certain how compliant the patients were. Unlike chronic medications, cessation products are usually for a short term use, so compliance should not be a significant problem [96]. (3) Some important variables were with missing information, for example, the stop dates of medications were sometimes missing and smoking status was not recorded regularly which may limit the

generalizability of our findings. Furthermore, information was not recorded in GE data for some possible confounders like education level, adherence to antipsychotic medications, with a recent loss, and nicotine addiction level (or how many cigarettes they smoke per day). We tried to infer nicotine addiction level from the NRT dosages they got but we would not be able to do so for those who were on Bupropion SR or Varenicline because the doses are fixed. Those who got Bupropion SR (Zyban) or Varenicline were assumed to have a high addiction as they did not go for the choice of easily accessible NRT. We might also underestimate the percentage of those on NRT and Bupropion. NRT usage might be under estimated because majority of products are over the counter. Smokers might not mention that information to their doctors if not being asked; therefore, it would not be recorded in GE EMR. As previously discussed, Bupropion (Zyban®) might be under estimated: depression is a common comorbid condition and physicians are more likely to prescribe Bupropion (Wellbutrin®) which is most likely being covered compared to Zyban®. Similarly, rates of suicide behaviors or attempts we found here in this study maybe underestimated if patients did not tell their doctors that they had suicide ideations or it was not recorded.

Despite these limitations, the population distribution in GE EMR is very similar with the US population and thus is representative of outpatient practice. It is also rich in clinical information including vital signs, laboratory results, medication list entries or prescriptions, and diagnoses or problems. With proper smoking status and smoking cessation medications (including NRT OTCs), it was considered an appropriate database for our research questions. No studies have been conducted with this population examining the associations between cessation medications and suicide attempts/behaviors. Our findings are important to fill the gap in research

as warnings were noticed for general populations and not properly examined in this minority sub-group who are already under higher risks.

CONCLUSION

Suicide is the leading cause of premature death among schizophrenic patients and some reports have been received regarding cessation medication exposures leading to suicide. Our study was the first to examine suicide behaviors or attempts among this minority population and we did not find any differences between the medications. Rates of suicide ideations/behaviors were 2.65% within one year after the exposure. The only predictor we found to be associated with suicide was comorbidity index. Healthcare providers should pay close attention for all the possible signs of suicide among this high risk population, especially those who are on pharmacological cessation intervention trying to quit smoking.

SUMMARY OF DISSERTATION

This was the first retrospective study that examined comparative effectiveness of smoking cessation medications among schizophrenic smokers. This included comparing effectiveness in leading to smoking abstinence as well as preventing the development of metabolic syndrome risks and suicide risks. Quitting smoking among schizophrenic smokers is important because they have a higher smoking prevalence and nicotine addiction level compared to the general population. Overall, in our study, we found the abstinence rate was about 18.02% at week 12 and 17.20% at year 1. Among those who quit at 12^{th} week, about 75.22% of the quitting effect sustained at 1 year. We did not find any differences between cessation medications after 12 weeks and 1 year of cessation treatment. However, those who were prescribed more than one medication within the 12 weeks had slightly lower chances of quitting with the effect almost reached the significance level. Other predictors

we found that were associated with quitting included being older, white, whose residential area was in the west part of U.S., and without smoking counseling. Patients who reported not smoking at week 12 and who did not receive cessation medications during week 16 to year 1 were more likely to be abstinent from smoking at year 1.

After excluding those who had diabetes, hyperlipidemia, or hypertension prior to cessation medications, we had 580 schizophrenic smokers. Among those, nearly half (n=276, 47.59%) developed one or more criteria of the metabolic syndromes within just one year after the treatment. We found that smokers who were prescribed NRT were less likely to develop metabolic syndromes as compared to those who were prescribed Varenicline. Other predictors we found that were associated cardiovascular risks included being male gender, and with higher levels of BMI and comorbidity index.

Suicide is the leading cause of premature death among schizophrenic patients. Rates of suicide ideations/behaviors were 2.65% within one year after the exposure. We did not find any differences in leading suicide between the medications. The only predictor we found to be associated with suicide was comorbidity index. Healthcare providers should pay close attention for all the possible signs of suicide among this high risk population, especially those who are on pharmacological cessation intervention attempting to quit smoking.

Predictors identified in this study should be considered when designing smoking cessation interventions. This minority population may need more tailored approaches to achieve a successful cessation outcome. Further, physicians are advised to carefully weigh the risks against the benefits before prescribing cessation medications since risks for metabolic syndromes and suicide were found to be very high. Healthcare providers should monitor patients' lab data regularly and pay close attention to all the possible signs of suicide thoughts among this high risk

population, especially those who are on pharmacological cessation intervention attempting to quit smoking.

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Appendix A. Search Strategy for the four databases

OVID MEDLINE

Vendor	Ovid
Database	Medline®
Date searched	10/04/2012
Database update	1996 to September Week 4 2012
Database searcher	I-Hsuan Wu

1	Smoking/
2	exp Tobacco/
3	(tobacco or smoking or cigar*).ti,ab.
4	Tobacco Use Disorder/
5	or/1-4
6	(quit* or cessation or stop or cease).ti,ab.
7	5 and 6
8	exp "Tobacco Use Cessation"/
9	Smoking/th [Therapy]
10	7 or 8 or 9
11	exp Schizophrenia/
12	(psychosis or psychotic or schizo*).ti,ab.
13	11 or 12
14	10 and 13
15	limit 14 to yr="2010 - 2013"

PUBMED (National Library of Medicine)

Vendor	NLM
Database	PubMed
Date searched	10/04/2012
Database searcher	I-Hsuan Wu

1	Smoking[mesh:noexp]
2	Tobacco[mesh]
3	tobacco[tiab] OR smoking[tiab] OR cigar*[tiab]
4	Tobacco Use Disorder[mesh:noexp]
5	#1 OR #2 OR #3 OR #4
6	quit*[tiab] OR cessation[tiab] OR stop[tiab] or cease[tiab]
7	#5 AND #6
8	Tobacco Use Cessation[mesh]
9	Smoking/therapy[Mesh]
10	#7 OR #8 OR #9
11	Schizophrenia[mesh]
12	psychosis[tiab] OR psychotic[tiab] OR schizo*[tiab]
13	#11 OR #12
14	#10 AND #13
15	2010:2013[edat]
16	#14 AND #15

Embase (Ovid)

Vendor	Ovid
Database	Embase®
Date searched	10/8/2012
Database update	1996 to 2012 week 40
Database searcher	Helena Vonville

1	smoking/ or "smoking and smoking related phenomena"/ or cigarette smoking/ or smoking habit/
2	tobacco/ or exp tobacco dependence/
3	smokeless tobacco/
4	(tobacco or smoking or cigar*).ti,ab.
5	or/1-4
6	(quit* or cessation or stop or cease).ti,ab.
7	5 and 6
8	smoking cessation/ or smoking cessation program/
9	smoking/th [Therapy]
10	tobacco dependence/th [Therapy]
11	or/7-10
12	exp schizophrenia/
13	(psychosis or psychotic or schizo*).ti,ab.
14	12 or 13
15	11 and 14
16	limit 15 to yr="2010 - 2013"

PsycINFO (Ovid)

Vendor	Ovid
Database	PsycINFO®
Date searched	10/8/2012
Database update	2002 to October Week 1 2012
Database searcher	Helena Vonville

1	tobacco smoking/ or nicotine/ or nicotine withdrawal/ or smokeless tobacco/
2	(tobacco or smoking or cigar*).ti,ab,id.
3	1 or 2
4	(quit* or cessation or stop or cease or abstinen*).ti,ab,id.
5	exp Drug Therapy/
6	4 or 5
7	3 and 6
8	exp Smoking Cessation/
9	7 or 8
10	exp schizophrenia/
11	(psychosis or psychotic or schizo*).ti,ab,id.
12	10 or 11
13	9 and 12
14	limit 13 to yr="2010 - 2013"

Appendix B. Characteristics of trials for smoking cessation in people with schizophrenia

Trials		Date of the trial	Drug, dose and duration (treatment group)	# Participants Rx group	Gender in Rx group	Age in Rx (S.D)	Race	Baseline PANSS score in Rx
		Location	Control group	# Participants control group	Gender in control group	Age in control (S.D)		Baseline PANSS score in control
NRT	Chen (2012)	06/2005 – 12/2006	High dose NRT: 31.2mg for first 4 weeks then 20.8mg for 4 weeks	92	86 M and 6 F	46.6 (9.8)	n/a	59.2 (13.8)
		Taiwan, Multi-center	Low dose NRT: 20.8mg for 8 weeks	92	85 M and 7 F	45.4 (11.0)		61.6 (16.0)
Bupropion SR	Bloch (2010)	n/a	14 week Bupropion SR 300 mg/d (150 mg/d for first 3 days) + cognitive behavior group therapy	21	17 M and 4 F	42.6 (10.6)	n/a	71.6 (22.5)
		n/a	Placebo + cognitive behavior group therapy	11	6 M and 5 F	44.5 (8.4)		68.3 (23.8)
Varenicline	Weiner (2011)	n/a	12 weeks Varenicline 1mg/d BID	4	n/a	n/a	n/a	n/a
		n/a	Placebo 12 weeks	4				
	Wiliams (2012)	5/8/2008 – 04/01/2010	12-week Varenicline 0.5mg/d first 3 days then BID next 4 days, then BID 1mg/d week 2-12	84	65 M and 19 F	40.2 (11.9)	75 W, 38 AA, 6 Asian, and 8 Other	55.9 (9.5)
		US and Canada	Placebo 12 weeks	43	33 M and 10 F	43.0 (10.2)		54.5 (10.7)
Studies from a previous Cochrane review								
Bupropion SR	Evins (2001)	n/a	Bupropion SR 150 mg/d for 12 weeks + 9 weekly 1 hr sessions of group CBT	9	6 M and 3 F	45.5 (7.2)	16 Whites 2 AA	n/a
		n/a	Placebo for 12 weeks + 9 weekly 1 hr sessions of group CBT	9	5 M and 4 F	42.7 (7.9)		n/a
	Evins (2005)	08/1999 – 03/2003	Bupropion SR 300 mg/d for 12 weeks+ 12 weekly 1 hr sessions of group CBT	25	19 M and 6 F	46.0 (9.4)	n/a	59.27 (14.45)
		US, Multi-center	Placebo for 12 weeks + 12 weekly 1 hr sessions of group CBT	28	20 M and 8 F	45.5 (8.3)		59.00 (12.03)
	Evins (2007)	06/2002 – 02/2004	Bupropion SR 300 mg/d for 12 weeks (150 mg/d for the first 7 days) + 12 weekly 1 hr sessions of group CBT + nicotine patch from week 4 (21mg/d for 4 weeks, then 14mg/d for 2 weeks, 7mg/d for 2 weeks + up to 18 mg/d nicotine gum as required)	25	n/a	44.8 (9.2)	n/a	61 (14)
		Multi-center	Placebo for 12 weeks (150 mg/d for the first 7 days) + 12 weekly 1 hr sessions of group CBT + nicotine patch from week 4 (21mg/d for 4 weeks, then 14mg/d for 2 weeks, 7mg/d for 2 weeks + up to 18 mg/d nicotine gum as required	26	n/a	43.6 (10.9)		67 (20)

PANSS: positive and negative syndrome scale

Appendix C. Summary of the outcome measures and results

Trials		Outcome - abstinence		
		Definition of abstinence	Abstinence reporting method	Abstinence results
NRT	Chen (2012)	Seven-day point prevalence abstinence at week 8	Self report + verified with expired CO<10ppm	No significant differences in abstinence between the two groups: 4 in the low dose group and 1 in the high dose group achieved abstinence at week 8
Bupropion SR	Bloch (2010)	Not smoking at the end of the treatment (14 weeks)	Self report	Subjects receiving Rx did not show significant differences in smoking behavior when compared to placebo
Varenicline	Weiner (2011)	Not smoking after 9, 10, 11, and 12 weeks of the treatment	Self report + verified with expired CO<10ppm	3/4 in Rx and 0/4 in placebo were considered abstinence at each time point (p=0.14)
	Wiliams (2012)	Seven-day point prevalence abstinence at week 12	Self report + verified with expired CO<10ppm	16/84 in Rx vs. 2/43 in placebo (p=0.046) achieved abstinence
Studies from a previous Cochrane review				
Bupropion SR	Evins (2001)	Not smoking at weeks 12	Self report + verified with expired CO<9ppm or serum cotinine <14ng/ml	3/9 in Rx and 1/9 in placebo achieved abstinence
	Evins (2005)	Seven-day point prevalence abstinence at week 12	Self report + verified with expired CO<9ppm	4/25 in Rx (16%) and 0/28 (0%) in placebo achieved abstinence (p = 0.043)
	Evins (2007)	Seven-day point prevalence abstinence at week 12	Self report + verified with expired CO<8ppm	9/25 (36%) in Rx group and 5/26 (19%) in placebo achieved abstinence, OR= 2.4 (0.66-8.4)